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Chemical Contaminants in Nonoccupationally Exposed U.S. Residents

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CHEMICAL CONTAMINANTS IN NONOCCUPATIONALLY EXPOSED U.S. RESIDENTS

by

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Archives of Environmental Health
Bulletin of Environmental Contamination and Toxicology
Drug Metabolism and Disposition
Environmental Health Perspectives
Environmental Research
Food and Cosmetics Toxicology
International Journal of Environmental Studies
Journal of Agricultural and Food Chemistry
Journal of Occupational Medicine
Journal of Toxicology and Environmental Health
Pesticides Monitoring Journal
Toxicology
Toxicology and Applied Pharmacology
Toxicology and Environmental Chemistry Reviews

Abstract Journals

- *Biological Abstracts*
- *Chemical Abstracts*
- *Excerpta Medica*
  - *Public Health*
  - *Pharmacology and Toxicology*
- *Index Medicus*
- *Nutrition Abstracts and Reviews*

Computerized Data Files

- MEDLINE
- TOXLINE
- DIALOG®
  - Agricola
  - Chemical Abstracts
  - Commonwealth Agricultural Bureaux
  - Environline
  - Food Science and Technology
  - Pollution Abstracts
- ORNL Data Base
  - Biological Abstracts/Research Index

Other

- Document collections of the Information Center Complex, Information Division, Oak Ridge National Laboratory
- National Academy of Science Monographs
- Reference document bibliographies
- *Trace Substances in Environmental Health*, Volumes I-IX, Proceedings of Annual Conferences held at the University of Missouri

FOREWORD

The many benefits of our modern, developing, industrial society are accompanied by certain hazards. Careful assessment of the relative risk of existing and new man-made environmental hazards is necessary for the establishment of sound regulatory policy. These regulations serve to enhance the quality of our environment in order to promote the public health and welfare and the productive capacity of our nation's population.

The Health Effects Research Laboratory, Research Triangle Park, conducts a coordinated environmental health research program in toxicology, epidemiology, and clinical studies using volunteer subjects. These studies address problems in air pollution, nonionizing radiation, environmental carcinogenesis, and the toxicology of pesticides as well as other chemical pollutants. The Laboratory participates in the development and revision of air quality criteria documents on pollutants for which national ambient air quality standards exist or are proposed, provides the data for registration of new pesticides or proposed suspension of those already in use, conducts research on hazardous and toxic materials, and is primarily responsible for providing the health basis for nonionizing radiation standards. Direct support to the regulatory function of the Agency is provided in the form of expert testimony and preparation of affidavits as well as expert advice to the Administrator to assure the adequacy of health care and surveillance of persons having suffered imminent and substantial endangerment of their health.

This report traces the sources of chemical contaminants derived from environmental pollutants from the environment to man. The summaries of the pathways and ultimate incidence and effect of these contaminants on man and the documented references should be very useful to researchers and others who are concerned about this ever-increasing problem of industrialized societies.

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ABSTRACT

This report reviews the manner in which chemical contaminants found in nonoccupationally exposed U.S. residents enter the environment and subsequently human tissues. Approximately 100 contaminants are treated. References used in the survey cover a 30-year period, with the bulk of the studies coming from the past 10 or 15 years.

Contaminants discussed include organochlorine, organophosphorus, carbamate, and miscellaneous pesticides; polychlorinated and polybrominated bi- and terphenyls; halogen compounds; asbestos; mercury, lead, zinc, cadmium, copper, manganese, molybdenum, selenium, arsenic, antimony, thallium, chromium, cobalt, nickel, vanadium, beryllium; and others. Production; use; entry into the environment; entry, metabolism, and effects in man; and description and evaluation of methods of analysis and of the validity of the data are the chief aspects treated. For the pesticides indiscriminate use is the chief means of environmental entry. Entry into man is by ingestion of particulate residues and through foods, particularly fat-containing animal products. Sources of environmental entry for the metals and other elements are burning of fossil fuels, industrial operations, dissipative uses, and natural inputs; and from these sources into man by ingestion and inhalation.

Some elements are essential or beneficial at one level of concentration and toxic at another. Discussions of the status of elements from this standpoint are included where appropriate.

SECTION 1

INTRODUCTION

1.1 LEGISLATIVE REQUIREMENT

Preparation of this report was directed by the Health and Environmental Studies Program, Information Center Complex, Information Division, Oak Ridge National Laboratory, for the Health Effects Research Laboratory, U.S. Environmental Protection Agency, as partial fulfillment of Interagency Agreement DOE No. 40-673-78, EPA No. 78-D-X0205, between the Department of Energy and the U.S. Environmental Protection Agency. The scope of this report is designed to complete the obligation of the U.S. Environmental Protection Agency as specified in Sections 403c(1) and 403c(2) of the Clean Air Act as amended August 7, 1977. These sections provide for the following:

> (c)(1) Not later than twelve months after the date of enactment of this Act the Administrator of the Environmental Protection Agency shall publish throughout the United States a list of all known chemical contaminants resulting from environmental pollution which have been found in human tissue including blood, urine, breast milk, and all other human tissue. Such list shall be prepared for the United States and shall indicate the approximate number of cases, the range of levels found, and the mean levels found.
>
> (c)(2) Not later than eighteen months after the date of enactment of this Act, the Administrator shall publish in the same manner an explanation of what is known about the manner in which the chemicals described in paragraph (1) entered the environment and thereafter human tissue.

The requirement of Section 403c(1) was satisfied by the publication in August 1978 of the preliminary report, ORNL/EIS-142, entitled "Levels of Chemical Contaminants in Nonoccupationally Exposed U.S. Residents." That report contained data on the human tissue levels of 94 different chemicals which leave residues in the human body. The compilation concerned mainly trace metals and organochlorine pesticides. Nearly 400 cited surveys or investigations, the majority of which were reported in the last decade, were listed. The tables in the compilation included information on the tissues in which the substances were found; the range; mean or median levels; number of cases; analytical methods used; comments on the source of the samples and on demographic and socioeconomic and geographic factors, and on any other special conditions; and the references.

Most of the available data examined for the purposes of the preliminary report resulted from specific surveys to determine the tissue levels of chemicals perceived to be potential health hazards or from incidents of accidental poisonings. Basic interest in the roles of trace elements and recognition of the need to determine baseline levels of chemicals introduced into the environment are additional factors which have motivated surveys by individual investigators. Data on a number of elements, known to be essential or beneficial at one level but harmful at another, were also included, as were data on some uncommon chemicals included as items of interest and to document their presence in healthy individuals.

To fulfill the stated requirement of Section 403c(2), this document includes the following factors to the extent that appropriate information was found:

A. Uses and sources. Production figures.

B. Entry into the environment. Transport and transformation processes. Effects on the environment.

C. Entry into man. Storage, disposition, effects. Demographic, geographic, and socioeconomic factors.

D. Evaluation of the analytical measurement methods and of the validity of the reported body burden data.

These aspects are covered as systematically as possible. In addition, in each section an attempt is made to present a picture of the status of the substance or class of substances in question, for further understanding of the role of the substances as possible pollutants. Information on some of the aspects listed above is sparse for a number of the substances, and where little is said about a particular aspect, it may be concluded that little information on it was found.

A section of the report covers the aspects of entry of contaminants into the environment, transport and transformation, and entry into humans and effects in humans in general. Similarly, there is a general section on analysis, in which the evolution of techniques, their sensitivity and reliability, and application to problems of monitoring contaminants are discussed. Special problems with analysis of particular contaminants, where these exist, are discussed in the appropriate sections.

1.1.1 Time Coverage

References in the preliminary report provided coverage of available information over the past 15 years (see "Sources of Data," p. vii). For the present document, and to check values given in the phase I report, literature coverage was extended to cover the past 30 years. No additional material which would significantly change the range of levels and means already reported was found. Some supplementary data, however, not obtained in time for the August deadline, have been added to a final version of the preliminary report, which is published as a companion document to this one.

1.1.2 Bibliographies

Bibliographies are included with each of the volumes. There is, therefore, some duplication in that significant references of the preliminary report have also been used here, plus references that were used because of the special requirements of this second phase of the project.

1.1.3 Selection and Grouping of Contaminants

Body burdens of 94 elements or compounds were listed in the preliminary report. For the present document, we have added several to this from the class of miscellaneous compounds which show up in the body and may have effects, but on which clear data on body burdens were not available. A section on organophosphorus and selected miscellaneous pesticides has also been added. The substances of the report are grouped into 13 sections. This grouping was governed by a number of considerations: convenience, similar chemical nature, similar mode of entry into the environment, similar geographic distribution or use pattern or other association, similar mode of entry into the body, and so on, for reasons of economy in writing and to give as balanced a picture as possible. Aspects treated, to the extent information was available, have been listed above.

SECTION 2

POLLUTION: GENERAL CONSIDERATIONS

"Polluted air + polluted water + polluted food = polluted people" (Ferren, 1978).

It is convenient to consider here some general aspects of pollution, which apply to all the contaminants listed. These include pathways of exposure, pathways in the environment, patterns of absorption and metabolism and rejection, and effects in humans and in the environment. The substances discussed in this report fall mainly into the classes of metals and a few other elements, and pesticides.

2.1 COMPOUNDS AND ELEMENTS AS POLLUTANTS

As stated by Ferren (1978), metals may well be the most harmful of pollutants, because they are not biodegradable and often have a long-term systemic effect. This statement may be controversial if compared, say, with the carcinogenic potential of certain organic substances; however, on a strict public health basis and in the context of this report, which deals with substances giving a body burden from long-term, low-grade pollution exposure, it is probably true. The situation with metals and with certain other elements is complicated by the fact that a number of them are essential to life or beneficial at one concentration but deleterious at another. As pointed out by Albert et al. (1973), all metals, even the essential ones, have the potential to cause adverse effects in human beings at certain levels of exposure and absorption.

Most of the compounds, as opposed to elements, treated in this report are pesticides.

Westermann (1969) has discussed the idea of "functional accumulation" of an environmental agent, i.e., accumulation of functional impairment. He gives the contrasting examples of DDT and organophosphorus pesticides. Because of a low rate of elimination and high fat solubility, DDT accumulates in man in fat deposits. According to Westermann, the average American adult has more than 50 mg of DDT in his or her body. However, the toxicity of DDT in mammals is low — toxic symptoms in man having been observed only at oral doses of 10 to 20 g. Organophosphorus pesticides are very toxic in man but do not accumulate substantially, since they are rapidly metabolized. However, small repeated doses show a distinct functional accumulative pattern, leading to clinical symptoms resembling strong cholinergic stimulation reflecting the pileup of acetylcholine at the cholinergic links in the organism, caused by inhibition of cholinesterase. Westermann gives other examples of functional accumulation or the lack of it and discusses some of the paradoxes of interference with function caused by exposure to contaminants. In the case of functionally accumulating contaminants, evidence of exposure may be sought by determining impairment or perturbation of function, or stimulation of new function (induction of enzyme activity, for instance), and this has been done.

With respect to body burdens, the extensive studies of the Tipton School (summarized by Perry et al., 1962) have shown that the concentrations of the nutritionally essential elements are more constant than the concentrations of the nonessential ones, within any selected group, and are also less affected by geographic differences, socioeconomic factors, and the like. Moreover, as remarked on by numerous authors and as studied in detail by Liebscher and Smith (1968), the distribution curve varies between essential and nonessential elements, essential elements having a symmetrical or "normal" distribution and nonessential ones a skewed or "log-normal" distribution. This is an expression of better homeostasis in the case of the essential elements, which is lacking or imperfect in the case of the nonessential ones.

With respect to changes in body burdens, Kist (1968) has studied the relation between the normal concentration of 17 elements in the body (using neutron activation) and their toxicity, i.e., the toxicity of experimentally added increments of the element. It was found that a relatively small increase in the concentration of a macroelement could lead to the death of the test animal. The reverse was true for elements contained in the body in very small quantities. In general, it was found that the lower the normal concentration of an element in the body, the greater the fluctuations in it from the standpoint of either an increase (toxicity) or a decrease (deficit) which can be tolerated by the body without noticeable harm. This fact applies, incidentally, in research trying to establish whether an element is essential (Schwarz, 1974; Mertz, 1970).

2.1.1 Man's Contribution

Schroeder (1965*b*) has discussed the distribution of trace elements over geologic time and the relation of this to life processes. Twelve bulk elements from the first 20 in the periodic table make up more than 99% of the structure of living things. Added to these are the trace elements selected by nature as micronutrients, their role being that of cofactors, nucleators, regulators, prosthetic groups for enzymes or other functional proteins (examples: zinc in carbonic anhydrase, copper in ceruloplasmin, etc.), the nonessential elements filling the role of accumulating environmental contaminants. In historical time, Schroeder shows how man has changed his exposure to both the essential and nonessential trace elements, depleting some elements and increasing others. With the onset of agriculture and the rise of civilization, ecosystems have been changed and forests denuded. Pastures have been overgrazed and soils overcropped. Foods are now highly processed, removing micronutrients at the same time that nonnatural substances are added to them. Nonessential elements have been mined from mineral deposits and introduced into the environment. Industry has released a wide spectrum of toxicants into the water (example: mercury) and into the air to be picked up by organisms in the food chain or to be absorbed as particulates. This nonnatural exposure has been going on since the Bronze Age, with exponential increase in the last 100 to 150 years. Aspects of this for individual elements are brought out in the appropriate sections.

2.2 PATHWAYS OF POLLUTANTS

2.2.1 In Animals

Spector (1956) gives a useful diagram and table of pathways of mineral metabolism in mammals. Information is given on 57 individual cations and 29 anions, with remarks on others. Although organics are not included, much of the information in the diagram applies to them too. Entrance into the organism, absorption, excretion, reabsorption, distribution, metabolic change, and retention are some of the aspects treated.

In the context of this report, the effects of toxic metals are largely due to their accumulation. This question has been investigated extensively by Albert et al. (1973). Aspects considered were the critical organ concept of toxicity and critical concentrations; absorption following intake by various routes; effects of age and condition on absorption, absorption by the fetus by placental transfer; transport and binding in blood and penetration into organs; gastrointestinal and renal and mammary gland excretion; accumulation and retention in critical organs; and concentrations in biological material as indices of exposure and of concentrations in critical organs.

Metal transport and effects in the body depend highly on the intrinsic nature of the metal, usually as an ion. The body may effect valence changes in the metal which will influence its behavior, and some metals are particularly susceptible to binding to certain chemical functions (heavy metals to sulfhydryl groups of proteins, for instance) or to coordination or inclusion in prosthetic groups or as part of the active site of an enzyme. Part of homeostasis may be the release of the metal on degradation of the protein. With organics, the picture can be complicated by the existence of degradation or modification of the structure of the molecule itself (examples: aryl epoxidation, ring opening, creation of new functions). Modification (usually by oxidation) may be a first step leading to elimination or to further metabolism. Unfortunately, the oxidation of organics may lead to products which are more deleterious than the original contaminant. Examples abound in the study of the conversion of procarcinogens to proximal and then to ultimate or actual carcinogens. If the conversion increases water solubility, makes conjugation possible, or leads quickly to innocuous products, then the contaminant may be eliminated before any great degree of this second-order type of harm occurs.

Pollutants may show associations and interrelationships. Some metals may be protective against others; for instance, zinc protects against copper. Both metals are essential, but excess of copper leads more easily to adverse effects. The protecting or controlling action may be rather broad. Thus, calcium has been considered as the "gatekeeper metal" (Schroeder, 1965*b*), controlling the absorption of other metals, both from the environment and across cell barriers. In the environment this action of calcium may depend on formation of insoluble salts, binding by soil, alkalinity, etc., and at the organismal level it has been postulated that there is a cellular mechanism, widespread among living things, which is saturated by calcium ion, regulating exchange of other cations from the immediate environment. Recent work has shown calcium to be associated with membrane phenomena, and the mechanisms therein may be the key to calcium's action.

In the body, both experimentally and in normal physiology, metals may be swept out by other metals that have similar activity and which occupy, grosso modo, the same physiological space. Where the sweeping-out does not occur, this is evidence that the metal has its own specific pathway or its own compartmentation. This was found to be the case with manganese (Cotzias and Greenough, 1958). In rats rendered low in manganese through feeding Mn-deficient diets, flooding with kindred metals (Co, Ni, Fe, V, Cr, Rh, Mg, Zn) failed to remove radioactive manganese; only manganese compounds were effective in this regard. This evident specificity may be contrasted with the apparent lack of specificity of the displacement, for instance, of bromide by chloride, molybdenum by tungsten, strontium by calcium, and others.

Sometimes fixation of an element to a cell constituent or structure, or compartmentation that sequesters the element, keeps it from being swept out. The latter is often the case with elements which concentrate in a slowly turning over tissue such as bone. An example of fixation in soft tissues is that of cadmium (Cotzias, Borg, and Selleck, 1961). In a study by these authors, even added cadmium did not sweep out fixed radioactive cadmium. Administration of zinc was also ineffective. Estimates of cadmium body burden have shown that cadmium concentrates in the kidney (Bonnell, Ross, and King, 1960, and other references in the section specifically devoted to cadmium), probably displacing zinc in certain organelles and at certain cellular binding sites (sulfhydryl-containing structures). Once bound, the cadmium does not respond to homeostatic signals, nor is it displaced by other metals. The obverse of sweeping out is penetration of a contaminant by the same means as used by an essential element. An example of this is thallium. Thallium is highly toxic; it is carried into cells because it follows the same pathways as does potassium and occupies the same physiological space (Emsley, 1978). In short, it mimics potassium. Presumably, potassium would displace thallium, but given the large amount of potassium in the body, this would be difficult to achieve.

2.2.2 In the Environment

This is a very ramified subject. Haque and Ash (1974) have considered the factors which affect the behavior of chemicals in the environment. They discuss water solubility and behavior in the hydrosphere; vapor pressure and behavior in the atmosphere; behavior in the lithosphere (adsorption, etc.); degradation, as by light, microbial action, etc.; and interaction with biota (uptake by plants, food chain transport, etc.). Information on pathways through the environment of a number of metals is given in a report of Wildung et al. (1974), and there are reports on specific elements, such as the one by Matti, Witherspoon, and Blaylock (1975) on the cycling of mercury and cadmium as typical pollutants in the environment.

It is important to know the environmental distribution of contaminants as well as body burdens. A holistic approach, rather than the vertical discipline approach of air quality, water quality, and aquatic ecology as is usually followed, is recommended by Ferren (1978). Ferren suggested that "Environmental analysis is optimized when the techniques used are simple and applicable to the maximum types of environmental samples at a minimum of cost." His report includes a model study of the metals zinc, cadmium, lead, and copper, in such diverse samples as human nails, dirt in nails, human hair, air and water samples, and clams, levels in the last sample representing the impact of polluted water upon the biotic food chain in the region studied (Staten Island, New York). In more agricultural regions, one would likely add samples from soils and plants. The metals were chosen as indicators of environmental pollution. The analytic technique used was that of anodic stripping voltammetry, meeting the criteria evoked in the quote. Clearly, more studies of this type are needed.

2.3 EFFECTS OF POLLUTANTS

2.3.1 Effects of Long-Term Low-Level Exposure in Man

The effects of contaminants at levels discussed here are often of a delayed nature and are not always directly obvious. Golberg (1972) has discussed this problem and has championed the study of what he calls "subliminal toxicology," meaning study of physiological indicators of effects of exposures at dose levels comparable with those to which the human population is actually being exposed. Some of the effects of toxicants are rather subtle. For instance, impairment of learning and behavioral problems have been noted in children exposed to lead, but whose blood lead levels were in ranges that had been considered "safe" or "normal." By the nature of the problem it is not easy to relate cause and effect, since factors other than the presence of the pollutant may play a role, or the presence of the pollutant may not be suspected. An example is the connection between drinking soft, slightly acid water and cardiovascular disease. There is some evidence that such water leaches certain metals, particularly cadmium, out of well pipes and water distribution pipes, and that the slightly elevated levels of these metals over normal contribute to hardening of the arteries, heart trouble, and other circulatory manifestations. Conversely, Bierenbaum et al. (1975), studying two groups of matched subjects of 260 persons each in the twin cities of Kansas City, Missouri (softened water) and Kansas City, Kansas (naturally hard water) found a higher incidence of coronary heart disease in subjects drinking the naturally hard water. In this case it was cadmium in the water source itself which seemed to be responsible for the hypertension causing the heart disease. This finding shows how all circumstances must be taken into account.

Effects are generally long term. Some authors have failed to appreciate this. An example is the statement of Ochsner (1967) in an editorial in a medical journal to the effect that "General air pollution, although not desirable, is usually not hazardous to health. It is dangerous only under unusual atmospheric conditions when excessive concentration of pollutants results from atmospheric inversion." Ochsner further said, "... and then the deaths have been almost without exception in patients who had preexisting pulmonary or cardiovascular disease, or both." Ochsner's views were refuted by Paulson and Zablow (1968), who pointed out a number of studies showing deleterious effects of air pollution on people not suffering from preexisting disease. Dubos (1968) also reacted to Ochsner's statements in the words, "The point of importance here is that the most significant effects of environmental pollutants will not be detected at the time of exposure to them; indeed, they may not become evident until several decades later. The greatest danger of pollution may well be that we shall tolerate levels of it so low as to have no acute nuisance value, but sufficiently high, nevertheless, to cause delayed pathological effects and to spoil the quality of life." In short, morbidity, but not necessarily mortality.

The delayed effects of air pollutants (since air pollution is one of the more prevalent forms of pollution) constitute models for the kinds of medical problems likely to arise in the future from all forms of pollution. Dubos also evokes effects on the fetus, only noted years later as reduced vigor, greater susceptibility to disease, and the like.

2.3.2 Effects on the Environment

The effects of chemicals on the environment have been considered by Goodman (1974). A good many of these effects have been unplanned. Persons have failed to consider what the real costs of introduction and widespread use of a new substance would be, or the real costs of careless disposal or release of contaminants. As pointed out by the author, failure to recognize the mutually interactive roles of man, resource species, wildlife organisms, and climate in the biosphere and their different tolerances to chemical substances has hindered the development of an environmental management policy embracing all four biosphere components.

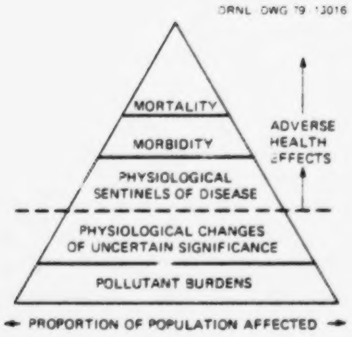
In the introduction to the symposium volume, "Survival in Toxic Environments," Hadley (1974) makes the point that we must move from a transient to a steady state in our global economy, from a youthful-exploitive to a mature quality-maintenance state. Poisoning of the environment must not be allowed to sabotage our achievement of this steady state. Intelligent use of ultimately limited resources requires a fundamental knowledge of the effects of waste contaminants on natural ecosystems, on the ecosystems created by man, and on man himself. To do this, it is necessary to bring together knowledge from a number of disciplines.

The question has been asked, "Are we already past the point of no return in some areas of pollution?" Even stopping introduction of the pollutant would not cause the harm to be undone. The possibility further exists of catastrophic expansion of some pollutants' potential for harm.

Mercury in Lake Erie has been given as an example. The accumulation there in sludges and in actual pools has been such that it is conceivable that a biotic bloom, caused by eutrophication, could convert the mercury at an accelerated rate to organic mercury, which could find its way up the food chain to the point of human consumption, and serious poisoning could ensue. Something like this happened in the Minamata incident in Japan; not from accumulation and triggering, but from such a rate of introduction of the pollutant into the environment (an ocean bay) that the biota in it were practically saturated, and a mass disaster resulted in an area where consumption of fish and other sea products was high. While further Minamatas and mini-Minamatas remain possible, the general situation is more likely to be deterioration of the type discussed by Dubos and by Paulson and Zablow. Mercury is, in fact, widespread, similar to DDT, to the point of making it necessary in some areas to limit the consumption of foods containing it.

In examining the references of this study, and in trying to determine geographic distribution of pollutants, it was noted many times that the effects of a pollutant were spread out over a wider geographic zone than the zone of introduction because of the ramification of food distribution. Melons grown in the All-American Valley in Arizona may well be sold in Philadelphia. Ice cream made in New York is sold in Tennessee, etc. Finished foods and raw materials for foods and animal feeds are shipped from one state to another and to other countries, not to mention what we import. Thus are pollutants distributed, but at the same time diluted, resulting in essentially a leveling of the pollutant concentration over large geographic areas. In some respects this may be good, as in the distribution of nutritionally essential elements (example: selenium, high in some areas, deficient in others).

The following diagram, due to Colucci et al. (1973), addresses the general question of pollutant burdens and biological response. The width across the triangle at a given level represents the proportion of population affected. From the mere presence of a pollutant or pollutants (the authors treat the question of multiple burdens), effects rise to changes of uncertain significance to changes which are indicative of disease, through morbidity to mortality. As pointed out by the authors, studies of multiple tissue sets and of levels in body fluids and of biochemical and physiological perturbations are all useful in assessing risk and response.


ORNL DWG 79 13016
MORTALITY
MORBIDITY
PHYSIOLOGICAL SENTINELS OF DISEASE
PHYSIOLOGICAL CHANGES OF UNCERTAIN SIGNIFICANCE
POLLUTANT BURDENS
ADVERSE HEALTH EFFECTS
PROPORTION OF POPULATION AFFECTED

Spectrum of biological response to pollutant exposure.

Adapted from Colucci et al., 1973.

SECTION 3

ANALYSIS

3.1 EVOLUTION OF METHODS

The Kirk-Othmer Encyclopedia of Chemical Technology (Grayson and Eckroth, 1978) lists a number of methods used in analytical chemistry, giving applications, theory of the test, advantages, sample size required, and method and sample limitations. Practically all these methods have been used in testing for and quantitating levels of contaminants. In extending our literature search to cover the past 30 years, the bulk of references found concerned methods of analysis. This period was in fact a time of concern over the effects of contaminants and a time of development in methods of analysis. Instrumental methods have come largely to the fore to replace chemical methods previously used. The modern methods are characterized by greater selectivity and by high sensitivity, bringing the limits of quantitation down in some areas to the ppb range. A recent development is the addition of microprocessors (for instance, with "floppy disk" control) to the analytical system, with advantages of feedback control and logic, reference storage, and printout of results. In this way, manufacturers are facing up to the problem of the increasing work load in the field of contaminant analysis as well as continuing to be concerned about the analyses themselves.

3.2 VALIDITY OF ANALYSES

Generally speaking, the methods used have given, or are capable of giving, valid results within the context of their proper use (awareness of the possibility of interferences, awareness of limitations of the method, etc.). Some improvement, and increase of confidence in the results, has come from use of methods whereby substances to be analyzed for are separated as an inherent part of the method of analysis and then quantitated. An example of this is gas chromatography. Another improvement has been in selectivity, and an example of this is atomic absorption spectrophotometry, where selectivity is obtained by exciting the atoms of an element with X-rays produced from a cathode of that same element. These points are further discussed in Section 3.4.

3.3 OBTAINING THE DATA

As important as the test itself is the whole context of the testing procedure. The Federal Working Group on Pest Management has published a document, "Guidelines on Analytical Methodology for Pesticide Residue Monitoring" (Monitoring Panel, FWGPM, 1975), which goes well beyond performance of the actual analysis. The concepts developed are applicable to testing of other substances in addition to pesticides. The same may be said for the companion volume, "Guidelines in Sampling and Statistical Methodologies for Ambient Pesticide Monitoring" (Monitoring Panel, FWGPM, 1974), which deals more specifically with testing for pollutants in the environment. The references in these two documents are invaluable. Topics treated in the document on analytical methodology include safety precautions to be taken by the analyst, sampling, storage of samples, extraction, cleanup, detection and quantitation, losses, metabolites and degradation products, the problems of analyzing for multicomponent pesticides, and evaluation and reporting of results. Included in the companion document are consideration of statistics and study design, and problems of obtaining samples for analysis of constituents in air, soil, and water, in animals, food, and feeds, and in man.

The above references concern pesticides. Anand, White, and Nino (1975) have considered errors which may occur in collection, storage, and analysis of trace elements in body fluids, and give recommendations for avoiding these errors.

The subject of instrumentation and methods used for monitoring metals in water has been reviewed by Quinby-Hunt (1978). Atomic absorption is the approved method (Code of Federal Regulations, Title 40, pt. 136) for most metals and metalloids. The author emphasizes the problems of doing meaningful monitoring at levels near the sensitivity of the method of analysis. Along with quantitative surveys, more attention to distinguishing species (compounds) of elements and further explorative qualitative surveys are recommended.

3.4 DESCRIPTION OF METHODS

3.4.1 Emission Spectrometry

Spark-source emission spectrometry was one of the early used instrumental methods. The extensive studies of Tipton et al. employed this method. These studies give protocols for the collection and handling of samples and for the analyses themselves. In this technique, samples are ashed and sparked in the emission spectrograph. A great number of elements are detected simultaneously. Detection is sensitive but quantitation is erratic; also, sample preparation is tedious. Reproducibility and precision can be improved by the use of ad hoc matrices to compensate for interferences and background noise.

Much of the problem with emission spectrometry has come from the spark activation. A recent development, reviewed by Fassel and Kniseley (1974*a,b*), is that of inductively coupled plasma-optical emission spectroscopy (ICP-OES). In contrast to spark-source emission spectrometry, the atoms of the sample are excited as a plasma by inductive heating. The sample need not be ashed. For instance, blood may be analyzed either directly or following dilution, and quite small samples may be analyzed. The technique is eminently suited to multielement analysis.

3.4.2 Mass Spectrometry

Heating is commonly used for mass spectrometry, but, particularly to volatilize elements, spark activation has also been used. An example is the study of Losee, Cutress, and Brown (1973) on the occurrence and concentrations of trace elements in human dental enamel. Enamel was ground and mixed with the graphite of the graphite electrode. Sixty-eight elements were analyzed for (with more possible); 38 were found in measurable concentration.

Mass spectrometry has been used for confirmation of results of some other systems of analysis, for instance, gas chromatography. Here part of the sample from the gas chromatograph is fed to the mass spectrometer, with the proper adaptors, for confirmation of the identity of the separated peak.

In a similar manner, Biros (1970) used nuclear magnetic resonance spectroscopy (NMR) for confirmation of identity and estimation of relative proportions of p,p'-DDT and p,p'-DDE isolated from adipose and liver tissue samples, not separated from each other by the gas chromatograph.

3.4.3 Atomic Absorption Spectrometry, Flame Photometry, Flame Emission Spectrometry

Atomic absorption spectrometry (AAS) is the technique which superseded spark emission spectrometry and is the technique approved for most of the elements. In this method, electrons of the element being analyzed absorb the X-ray emission line from a cathode of the same substance. A multielement cathode can be used, and multielement analyses can be done on a single sample. The method is in part an outgrowth of flame photometry, which in the modern form of flame emission spectrometry (FES) continues to hold its own for certain analyses. Improvements have come in the use of very high flame temperatures, impulse methods of sample evaporation, use of grating monochromators, and advances in the response system. Instrumentation for FES and instrumentation for AAS have aspects in common, and Prudnikov (1978) describes the two systems side by side. The systems in fact complement each other.

Flameless heating of a sample in a graphite cup or a graphite tube is now used for atomic absorption. The sample is atomized off by programmed heating into the light beam rather than being aspirated through a flame, as was the original case. The pitfalls, advantages, and applications of this technique have recently been reviewed by Robinson (1978). The technique is versatile but requires considerable skill. For the necessary short response time, digital electronics are used. Robinson also reviews the prospects for laser intracavity absorption for organic compounds. This is an application of infrared analysis, in which rotational vibrational spectra of molecules are being used, not electron transitions. To achieve narrow wavelength absorption, narrow laser emission bands (from a tunable laser) are used, thus making the technique selective in the same way that atomic absorption is selective with its narrow emission and absorption lines. In practice, the attenuation of the laser beam is measured. The technique is not limited to organic substances; metals, metal oxides, salts, free radicals, etc., can also be measured.

3.4.4 Neutron Activation Analysis

Neutron activation analysis, used in a number of the reports listed in the bibliography, is a highly general technique, useful for both qualitative and fine quantitative analyses of a wide spread of elements. It is applicable to both solids and liquids and requires minimal sample handling. The technique is nondestructive. The sensitivity varies considerably among elements, but for most is better than 1 μg. The sample is bombarded by neutrons, and then its gamma-ray spectrum is measured. A peak of a certain energy in MeVs is characteristic of the radioactive species produced from a given element by the neutron bombardment. For sharp identification, analyzers with a high number of channels are used. An example of the use of this technique is given by the study of Mahler et al. (1970) on trace metals in fingernails and hair. Since these are devitalized structures, they show the history of exposure. Manganese, copper, gold, and zinc, plus other elements, were easily quantitated.

3.4.5 Gas Chromatography

For organics, gas chromatography has been a revolution. To the separation of the substances, already giving a high degree of selectivity, has been added the sensitivity of specific detection, such as electron-capture detectors for compounds which have a high electron affinity. Since halogenated compounds are included in this class, the application to organochlorine pesticides, such as DDT and its metabolic products, is obvious. If the compound does not show electron affinity, it can be added by derivatization, for instance, by trifluoroacetylation, which in any case may be necessary to confer volatility on the substance for the gas chromatographic process. Bente (1978) has recently reviewed the state of the art in electron-capture instrumentation and its application to toxicology. Numerous ingenious tricks are applied, such as pulsing the voltage, changing the frequency, and so on, to promote selectivity and to extend the range of analyses. Gas chromatography may require cleanup of the sample, for example, by column or thin-layer chromatography, before an extract is presented to the final chromatographic system.

3.4.6 High-Pressure Liquid Chromatography

A technique which is rapidly coming to the fore and which is displacing gas chromatography for some applications is that of high-pressure or high-performance liquid chromatography. Both partition and adsorption modes are used. An advantage of HPLC over gas chromatography is the lack of thermal degradation of compounds because of the absence of a need for temperature programming. Further, the sample need not be volatile nor rendered volatile by derivatization. Some applications have been analysis of PCBs, aromatic pesticides, nitrosamines, etc. (Tracor, Inc., 1978).

3.4.7 Other Methods

X-ray fluorescence and electron-probe microanalysis have been used for certain situations. Specific-ion electrodes are useful for analysis of some elements and species, for instance, fluorine. Fluorescence and fluorescence quenching are used for some elements and compounds. Polarography and particularly anodic stripping voltammetry (reverse polarography) are useful for certain elements. Spot tests are useful for screening. Thin-layer chromatography is useful for both cleanup and actual analysis and can handle a large number of samples.

An example of how techniques must sometimes be coupled to solve a problem in analysis is given by Talmi and Norvell (1975). These authors were analyzing environmental samples for arsenic and antimony. Samples were wet-ashed with nitric-perchloric acid, the As^{3+} and Sb^{3+} formed were then cocrystallized with thionalid, and the precipitate formed was reacted with phenyl magnesium bromide to form triphenyl arsine and stibine. These were extracted with ether and subjected to gas chromatography. Detection was by a microwave emission spectrometric system. Thus the arsenic and antimony were carried through the stages of from molecular compound or whatever state they were in in the samples to ionic species to organic compound for separation, to the atomic state for final readout. A wide range of samples was analyzed with good precision and reproducibility.

3.4.8 Biological Tests

Biological tests are little used for direct analysis; however, they are sometimes used partly for indirect analysis and partly to show the significance of the level of a pollutant. Examples are examination of nerve-enzyme activity for indication of the degree of exposure to, and burden of, organophosphate pesticides, and measurement of delta-aminolevulinic acid dehydratase activity (the enzyme and the compound being important in porphyrin metabolism) for estimation of the degree of intoxication by lead. Functional, neurological, and behavioral (learning, response to tasks, etc.) are tests which have their place in epidemiology, but less so in direct testing. Immunological tests have practically not been used. However, they are used in the clinic for compounds (generally those with a low therapeutic index such as digitoxin) that are not all that different from compounds which, if not now pollutants, may well become so (such as complicated organics from fossil fuel conversion). The difficulty is that antibody to haptenized antigen (the pollutant being the hapten) must be developed, standardized, etc., and this is a cumbersome process.

In testing for pollutants in the environment, often what we need to know is the activity of the pollutant vis-à-vis transport and transformation processes, and availability to and effects on plants and microorganisms. Here biological tests can be useful. An example is the study of Henkens (1961), who compared biological and chemical tests for the copper content of soil. Growth of the mold *Aspergillus niger* was used for the estimation of the biological activity of copper.

Other specific tests and classes of tests not mentioned here appear in the bibliographies and in the discussion of specific elements and compounds. These are less often used than the tests described.

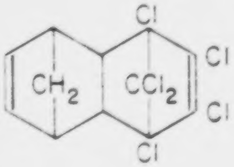
SECTION 4

ORGANOCHLORINE PESTICIDES

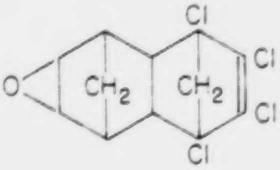
Organochlorine pesticides are of concern because of their persistent nature. We discuss the ones listed in the preliminary report of this project in alphabetical order, except when one pesticide is closely related chemically to another, for example, aldrin and dieldrin.

4.1 ALDRIN AND DIELDRIN

Aldrin is 1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-exo-1,4-endo-5,8-dimethanonaphthalene:



Dieldrin, also called HEOD or hexachloro-epoxy-octahydro-endo,exodimethanonaphthalene, is the epoxide of aldrin:



Aldrin is moderately soluble in aromatics, esters, halogenated solvents, ketones, and paraffins, and sparingly soluble in alcohols. It is insoluble in water. Dieldrin is also soluble to varying degrees in organic solvents and is insoluble in water. Aldrin is used to control soil insects and also termites. It is not greatly harmful to plants or to soil microorganisms. It can be absorbed by ingestion or by inhalation, but the greatest occupational hazard is skin absorption. Dieldrin also is used for the control of soil insects, public health insects, termites, etc. Aldrin is converted in the body to dieldrin, and the body burden of dieldrin is a reflection of the intensity of exposure to both dieldrin and aldrin (Hunter and Robinson, 1968). The level in adipose tissue is more precise for definition of body burden than blood-level estimations. According to Hodge et al. (1967), typical diets in England and the U.S. are estimated to contain 0.001 to 0.002 ppm dieldrin. Patients showing signs of intoxication had blood levels exceeding 20 μg/ml. Mick et al. (1971) have studied the transport of aldrin and dieldrin in the blood, and particularly the shuttling of these two pesticides between α- and β-lipoprotein fractions, the plasma, and the erythrocytes as the aldrin-dieldrin is carried to storage in adipose tissue. Aldrin crosses the placenta (Selby, Newell, Hauser, and Junker, 1969). Following oxidation to dieldrin, aldrin is excreted largely in the feces (Quaife, Winbush, and Fitzhugh, 1967). Production of both aldrin and dieldrin has been discontinued in the U.S. The level of use of aldrin in 1977 was 11,528,170 lb, crops treated with it being corn, grain, lettuce, sorghum, tobacco, tomatoes, and vegetables, pretty much all over the U.S. (U.S. Environmental Protection Agency, 1978), and use of aldrin and dieldrin in combination was 74,200 lb.

4.2 ENDRIN

Endrin is isomeric with dieldrin, differing in the orientation of the epoxide group. The usage of endrin in the U.S. in 1977 was 1,269,570 lb. Of this, 1,166,573 lb was used on cotton and the rest on orchard fruits and small grains. Curley et al. (1970) have reported on measurement of endrin in the blood, tissues, and urine of patients poisoned by consumption of products made from endrin-contaminated flour.

4.3 BENZENE HEXACHLORIDE

Benzene hexachloride (BHC, $C_6H_6Cl_6$), is not a compound of benzene but of cyclohexane. It should not be confused with hexachlorobenzene, C_6Cl_6, which is used for treatment of seed to prevent molds and kill insects, and is often used in combination with other pesticides, including BHC. Five isomers of BHC are commonly found in technical BHC (Meister et al., 1977, p. D36). The γ-isomer has by far the most activity. The grade of BHC in which the content of γ-isomer is over 99% is known as lindane. Mixed grades are also used. The BHCs are soluble in benzene and chloroform and in oil-base solvents, but are practically insoluble in water. The BHCs do not have as long a residual action as DDT because of higher volatility (Meister et al., 1977). Lindane is odorless and has been used as a fumigant and in household pesticide applications. BHC has been much used against cotton insects, but has had limited use on food crops because of odor and off-flavor contributed to the crop. Usage of BHC in the U.S. in 1977 was only 1231 lb, and of lindane 323,736 lb (U.S. Environmental Protection Agency, 1978).

Samuels and Milby (1971) have studied the clinical, hematological, and biochemical effects of human exposure to lindane. Some slight perturbation of hematopoietic processes was noted. Lindane was found not to accumulate, but to reach a level reflecting recent exposure. In contrast to β-BHC, lindane is not retained in the body: it enters fatty tissue but is there in equilibrium with the blood (Samuels and Milby, 1971; Radomski et al., 1971). It is excreted in both feces and urine. Contrary to the relation between fatty tissues and blood, Dyment, Hebertson, and Decker

(1971) found a lack of correlation between blood levels of BHC in milk and in serum; thus, while milk indicates exposure, it is not a good indicator of body burden. As shown by Selby et al. (1969*a*) and by Curley, Copeland, and Kimbrough (1969), BHC crosses the placenta. Levels of lindane and other BHC isomers are higher among persons living under low socioeconomic conditions (Burns, 1974; Kutz et al., 1977; Deichmann and Radomski, 1968), explained by their living closer to the source of contamination (agricultural use) and because of a lower level of hygiene (unsanitary garbage disposal, attracting pests, which are then sprayed. etc.). Using values of pesticide levels from maternal blood and from placental and adipose tissues, and using data from questionnaires concerning exposure, Selby, Newell, Waggenspack, Hauser, and Junker (1969) attempted to correlate exposure to pesticides with their clinically measured levels, with inconclusive results; however, the methods developed would likely be useful in epidemiological studies if applied on a larger scale and with greater input of data. The "chemical index" was demonstrated to be a more logical choice than the "environmental index" for estimating pesticide intake with the chlorinated hydrocarbons studied. The situation might be different with less persistent pesticides.

In water supplies, BHC, because of its low water solubility, as is the case with other organochlorine pesticides, is concentrated in silt, sand, plankton, and algae (Schafer, 1968); in soils it may be adsorbed on clay particles. Soil organisms have a part in mobilizing such pesticides. In a study done in Czechoslovakia, Szokolay, Madaric, and Uhnak (1977) found a greater accumulation of β-BHC than of other isomers in the food chain, including animal food products. Levels of BHC isomers in the soil were lower than levels of DDT and DDE, but transfer of the BHC isomers to vegetables (potatoes) was higher than the transfer of DDT and DDE. Organochlorine pesticides are persistent in the environment; however, BHC is noteworthy because it disappears fairly rapidly in the soil, through dehydrochlorination and oxidation by soil bacteria (Matsumura, 1973). Alkalinity of the soil also aids degradation.

4.4 PENTACHLOROPHENOL

4.4.1 Uses and Effects

Pentachlorophenol (PCP) is a substance which has been widely used for the protection of wood and other fibrous materials against insects and molds. As well as the main substance, technical PCP also contains TCDD (tetrachlorodibenzodioxin, see Sect. 4.5), other dioxins and so-called "pre-dioxins," and chlorinated dibenzofurans, resulting from side reactions in manufacture. Cattle and hogs have become sick from gnawing wood treated with PCP. Fish kills have resulted, at a level of about 0.5 ppm PCP in water. Its use has been somewhat indiscriminate. Formulations for painting or spraying onto wood are available to homeowners. Pentachlorophenol itself is toxic. An epidemic resulting in two deaths occurred in a nursery in St. Louis after the use of PCP as a mildew preventive with the laundry detergent (Barthel et al., 1969). Other cases of poisoning are reported in the Episode Summary reports, some at the worksite or during construction activities, others at schools, the home, etc. Symptoms of poisoning are weakness, headache, double vision, tachycardia, nausea, hyperpyrexia, and skin and eye irritation. Liver damage results from chronic exposure. Absorption may occur by inhalation or through the skin, and less frequently by ingestion of PCP residues. Melnikov (1971) has discussed synthesis of PCP, use, the question of residues, and so on, and Bevenue and Beckman (1967) have discussed properties of PCP, its toxicology, analysis, and its occurrence as a residue in human and animal tissues. PCP is relatively long-lasting in wood, but is fairly readily degraded in soils and by sunlight; and it is partly excreted and partly metabolized in the animal body. PCP uncouples oxidative phosphorylation (Zalkin and Racker, 1965). PCP gives rise to the metabolite tetrachlorohydroquinone, which is a potent inhibitor of β-glucuronidase, a chief conjugating enzyme (Ahlborg, Lindgren, and Mercier, 1974). Tetrachlorohydroquinone in the urine is an indicator of exposure to PCP.

Aside from the uses mentioned above, PCP is highly phytotoxic and is used as a general weed killer and as a desiccant for crops before harvest, large quantities being used on, for instance, cotton. Copper pentachlorophenate has been much used as a molluscicide to control schistosomiasis.

4.4.2 Analysis

Analysis of PCP is generally by gas chromatography, by which method it may be detected in the urine in picogram quantities (Bevenue et al., 1966). Colorimetry (Ueda et al., 1969), turbidimetry (Comstock, Comstock, and Ellison, 1967), and chemical ionization mass spectrometry (Dougherty and Piotrowska, 1976) are also methods which have been used. Bevenue and Beckman (1967) also cite analysis by paper, thin-layer, and ion exchange chromatography, by various chemical colorimetric methods, and by ultraviolet and infrared spectroscopy.

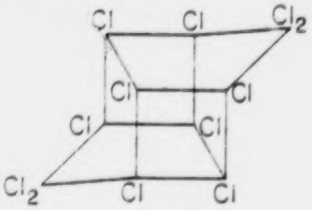
4.5 2,4,5-TRICHLOROPHENOXY ACETIC ACID

2,4,5-Trichlorophenoxy acetic acid (2,4,5-T) has one more chlorine atom than 2,4-D. It is more effective than 2,4-D in controlling brushy plants, and has been used in combination with 2,4-D for control of brushy and herbaceous plants. Properly used (avoiding drift, which would damage susceptible crops, avoiding entry into streams, etc.), the herbicide was thought to present no great danger. However, fish kills and fatal and acute incidents in humans and in domestic animals have occurred (U.S. Environmental Protection Agency, 1977*b*). The damage comes from the fact that 2,4,5-T contains a contaminant, TCDD, or 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. This is one of the most toxic synthetic substances known, the lethal dose for the guinea pig being of the order of 0.6 μg/g (Matsumura, 1974). In man, exposure to TCDD causes skin eruption and eye and respiratory tract irritation. Because fetal deaths and teratogenic effects have been shown in laboratory animals, they are also to be feared as possible effects in humans. Present as a contaminant, TCDD is also formed to a slight extent from 2,4,5-T by microbial degradation and is considerably more stable than 2,4,5-T. The extent to which it accumulates in the environment, however, is somewhat uncertain (Matsumura, 1974). In 1970, U.S. registration was canceled for granular 2,4,5-T formulations for use around the home, recreation areas, and similar sites (Meister et al., 1977, P. D252), partly because of concern over toxicity due to TCDD and partly because of the drift question. Usage of 2,4,5-T in 1977 (U.S. Environmental Protection Agency, 1978) was 995,703 lb, and of 2,4,5-TP (Silvex), the propionic acid analog of 2,4,5-T, 553,262 lb.

The EPA has considered 2,4,5-T as its most important pesticide decision (Anon., 1979) because of a possible link between exposure to 2,4,5-T from forest spraying and miscarriages in pregnant women and other health effects; human milk and urine samples from volunteers are being tested, plus other monitoring activities. The EPA has now halted most uses of 2,4,5-T and Silvex (Smith, 1979) because of the possible damage of miscarriages caused by TCDD in the two pesticides.

4.6 MIREX

Mirex is the completely chlorinated compound dodecachloro-octahydro-1,3,4-metheno-2H-cyclobuta[c,d]pentalene, characterized by contiguous tetra- and penta-chlorinated rings, as seen by the structural formula:



Mirex was developed particularly for use against the fire ant. It has also been used as a flame-protective coating. While it is of relatively low toxicity to birds, fish, and crustaceans (Martin and Worthing, 1974, p. 360; see, however, Waters, Huff, and Gerstner, 1977), it is extremely persistent, and detectable residues have been found in 2^% of adipose samples of persons living in mirex treatment areas in the southern states (Anon., 1978*a*).

Mirex seems not to be metabolized by mammalian systems; however, in experimental animals, treatment with mirex provoked mixed-oxidases activity and other physiological and biochemical responses (as cited in Waters, Huff, and Gerstner, 1977). Mirex crosses the placental barrier. It is excreted mainly in the feces, with small amounts in the milk and urine. Mirex is stored in tissues in the following decreasing order: fat, muscle, liver, kidney, and intestines (Mehendale et al., 1972).

4.7 KEPONE

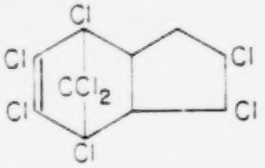
Kepone, or chlordecone, is the pentalen-2-one keto analog of mirex. The two chlorines at the peak of one of the pentalene rings are replaced by an oxygen. Kepone is present in mirex as an impurity and is also formed from it by oxidation; and it has been synthesized as an insecticide in its own right. Gas-liquid chromatography, with confirmation by mass spectroscopy (Harless et al., 1978), has been used for analysis of mirex and kepone. Bases for concern over the widespread use of mirex and kepone include: (1) adverse effects on reproduction as demonstrated in laboratory animals, (2) detectable amounts found in human adipose tissue, (3) tumorigenic implications in mice, (4) effects on mammalian energy metabolism, (5) effects on delayed mortality in birds, (6) potential to move in a saltwater environment (and high potential for bioconcentration), (7) effects on certain aquatic organisms, and (8) persistence.

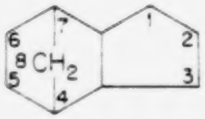
The production of both mirex and kepone has been discontinued. The Pesticide Usage Survey reports 133 lb used in 1977 on pineapples (U.S. Environmental Protection Agency, 1978).

4.8 CHLORDANE AND RELATED CYCLODIENE PESTICIDES

4.8.1 Chlordane

Illustrated below is the projected formula of chlordane; the formulas of the other pesticides may be derived from it. The numbering follows that of the 4,7-methanoindane structure shown:





Isomers differing in the positions and orientation of the chlorine groups exist, and may have different biological activity. Thus, Büchel and Fischer (1966) have claimed greater insecticidal activity and lower mammalian toxicity for the 2,2,4,5,6,7,8,8-octachloro isomer than for the normal one, which is 1,2,4,5,6,7,8,8-octachloro.

Isomerism at positions 1 and 2 gives two major classes of isomers, cis- and trans-. Technical chlordane is a mixture of about 70% cis- and 25% trans-isomers, with small amounts of other chlorinated molecules (Martin and Worthing, 1974, p. 95; Meister et al., 1977, pp. D57-D58). Chlordane is a nonsystemic stomach and contact poison with low phototoxicity. It has been formulated as granules, dusts, wettable powders, and in solution for making a water emulsion. Chlordane has a fairly high vapor pressure, but it is not easily degraded and, therefore, persists in the environment. One prominent use is for protection against termites. Savage (1975) has studied levels in soil and air around houses in connection with treating the soil for termites with chlordane and other cyclodiene pesticides, comparing levels around and in conventional houses with those of houses using the crawl space for a plenum or to enclose heating or cooling ducts. Blood samples of volunteers were also taken. The presence of the pesticides was detected, but at levels below those considered hazardous to health. The main use of chlordane is on crops. It is reported (U.S. Environmental Protection Agency, 1978) that 2,664,847 lb of chlordane was used in the U.S. in 1977 on a variety of crops. The manufacture of chlordane has, however, been discontinued in the U.S.

4.8.2 Oxychlordane

Oxychlordane, 1-exo-2-endo-4,5,6,7,8,8-octachloro-2,3-epoxy-2,3,3a,4-7,7a-hexahydro-4,7-methanoindene, is a metabolic oxidation product of chlordane. Piros and Enos (1973) reported the consistent finding of oxychlordane in general population human adipose tissue samples obtained through the National Human Monitoring Program (Yobs, 1971). Oxychlordane is a nonpolar compound, and thus is stored in fat. Levels were at 0.03 to 0.40 ppm; mean 0.14 ± 0.09 ppm. Kutz, Murphy, and Strassman (1978) give figures from a more extensive survey for FY's 1973 and 1974; maximum levels were 1.43 and 1.73 ppm respectively; (geometric) mean 0.12 ppm.

4.8.3 Heptachlor and Heptachlorepoxide

Heptachlor is 1,4,5,6,7,8,8-heptachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene, and heptachlorepoxide is an oxidation product of it, bearing an epoxy grouping at the 2,3 position of the parent structure. Heptachlor was first found as a contaminant in the production of chlordane; later it was synthesized as a pesticide in its own right. It is a waxy solid, practically insoluble in water but soluble in ethanol and in kerosene and other organic solvents. It is a nonsystemic stomach and contact insecticide with some fumigant action (Martin and Worthing, 1974, p. 291). The epoxide is formed by biological action in a wide variety of organisms, including man and other mammals, birds, and soil organisms. The epoxide is particularly persistent and biologically active. The Council for Agricultural Science and Technology (1975) stated that the half-life of heptachlor is about 0.8 year (chlordane 1 year) under agricultural conditions. Because of insolubility, chlordane and heptachlor tend to remain at the site of application and tend not to enter greatly into food chains; however, some can get into plants, and Richou-Bac (1974; in France) found significant levels of heptachlorepoxide in foods of animal origin, particularly milk and milk products, in a region showing regular augmentation of soil levels of heptachlor and heptachlorepoxide. Heptachlor is the most toxic pesticide which has been found for termites. Loss of heptachlor is mainly by volatility. Heptachlor and heptachlorepoxide cross the placenta and also appear in milk (Casarett et al., 1968). The two pesticides are eliminated mainly in the feces (Girenko, Kurchatov, and Klisenko, 1970). Usage of heptachlor reported in 1977 for the U.S. was 1,957,726 lb; the bulk, 1,344,159 lb, was used on corn land and the rest on other field crops and for seed treatment.

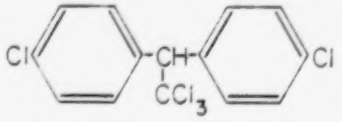
4.8.4 Trans-Nonachlor

Trans-nonachlor, 1,2,3,4,5,6,7,8,8-nonachloro-3a,4,7,7a-tetrahydro-4,7-methanoindane, is a component of technical chlordane and technical heptachlor. Kutz et al. (1976) have studied the geographical distribution of trans-nonachlor in human adipose tissue samples from subjects in the nine census regions of the U.S. The presence of this contaminant was confirmed at levels of about 0.01 to 0.10 ppm in all regions but one (East North Central) and at a lower level than others in one (Mountain). As reported by Kutz, Strassman, and Sperling (1978), the frequency of finding trans-nonachlor in human adipose tissue samples, which was 95.7% in FY 1974, was 96.8% in FY 1975, and the geometric mean in ppm had gone from 0.10 to 0.15. The finding of trans-nonachlor is indicative of exposure to chlordane and/or heptachlor. The metabolism of trans-nonachlor is not known, but is likely similar to that of heptachlor.

4.9 DDT

4.9.1 General and Historical

DDT is the common name of the technical mixture of isomers of 1,1,1,-trichloro-2,2-bis(chlorophenyl)ethane, or Dichloro Diphenyl Trichloroethane. The formula of the p,p'-isomer, which is the predominant and most greatly desired one, is given; the formulas of other isomers and of metabolites may be derived from it:



DDT was first described in 1874 by Zeidler, but its insecticidal activity was not uncovered until 1939 by Muller in Switzerland. It was brought into the U.S. for testing in 1942 and later imported in quantity, and by early 1944, domestic production for at first military use was under way (Meister et al., 1977, p. D80). DDT was a revolution in pest control. It seemed the perfect insecticide — highly toxic to insects (except for certain phytophagous mites), nontoxic to plants (except for the cucurbitae), nontoxic to warm-blooded animals, and inexpensive to produce. The benefits seemed largely to outweigh any risks, and fantastic quantities were produced for public health campaigns for the control of malaria and other insect-propagated diseases and for control of insects in general. It was estimated by Knipling (1953; cited in Edwards, 1973*a*,*b*) that during the first decade of use, DDT saved 5 million lives and prevented 100 million serious illnesses due to malaria and typhus, dysentery, and more than 20 other insect-borne diseases. Literally tons were used in agriculture, in forestry, in fogging city streets, and so on.

4.9.2 Persistence and Use

While DDT is fairly easily degraded chemically or by ultraviolet photolysis or by heating, in application the conditions necessary for degradation might not occur, and thus it is persistent in the environment. Further, it accumulates in food chains because of its low water solubility. Side effects of DDT include effects on birds and on their eggs, hormone stress, effects on ecosystems through killing of nontarget organisms, and actual dispersion of some insect pests by use of DDT through selection of dispersion as a trait. These effects, plus diminishing returns in use because of the buildup of resistant strains, finally became of such concern that after three years of intensive administrative inquiry (Kutz et al., 1977), all uses of DDT, except for emergency public health ones and a few others permitted on an individual basis, were prohibited in the U.S., effective December 31, 1972.

Use had already considerably declined. Kutz et al. (1977) show a graph of domestic use of DDT from 1950 through 1972. The peak use of 80 million lb was in 1959. Use from then on declined almost linearly, and in 1972 was about 12 million lb. The Pesticide Usage Survey (U.S. Environmental Protection Agency, 1978) reports 7100 lb of DDT used in the U.S. in 1977.

4.9.3 Levels in the General Population

Concurrent with the decrease in use of DDT has been a decrease in residue concentrations in humans (DDT and metabolites and congeners of DDT), particularly in younger age groups, as shown by the results of the EPA National Human Monitoring Program for Pesticides (Kutz et al., 1977). Total DDT equivalent residues in human adipose tissue decreased from 7.88 ppm lipid weight for general population samples in FY 1970 to 5.02 ppm in FY 1974, and in the 0 to 14 age group from 4.47 to 2.32 ppm. There was a slight rise in levels in the general population for FY 1975, probably without great significance (Kutz, Strassman, and Sperling, 1978). Other organochlorine pesticide residues, for example, benzene hexachloride, dieldrin, heptachlor epoxide, oxychlordane, and trans-nonachlor, did not show the same decline as DDT; in fact, some went up. Note that use of these other pesticides was restricted later than the use of DDT. Samples from blacks contained almost twice as much total DDT equivalent residues as samples from whites, reflecting the respective socioeconomic situations of these two population groups.

Some representative studies may be mentioned. For instance, in Dade County, Florida, Davies et al. (1972) studied the effect of five socioeconomic classes on pesticide levels. The classes involved occupation, income, housing, and education. Lower classes had higher levels of DDT and DDE; and with similar indicators, blacks had higher levels than whites. Arthur et al. (1975) studied serum pesticide levels in the general population of Mississippi. Blacks again had higher levels, and their total protein, alkaline phosphatase, lactic dehydrogenase, and glutamic-oxalacetic transaminase values were higher than in whites; this demonstrated greater impact of the pesticides on the blacks because of their relatively disadvantaged living conditions and possibly also reflected differing dietary regimes.

4.9.4 Sources and Entry into Man

There is some disagreement as to which is the main source of intake of DDT by man — food or dusts. The intake from water is very low. The answer may depend on whether one is speaking generally or of particular situations. Thus, Campbell, Richardson, and Schafer (1965) considered that food contributed over 90% of the DDT absorbed by people in the general population. Likewise, Sharman (1973) has considered the main sources of residues of organochlorine pesticides to be meat, fish, poultry, and dairy products and has advocated the reduction of the consumption of contaminated feed as the most effective way of reducing human intake of such residues. On the other hand, other authors dealing with specific situations have shown that the intake from dusts, whether household dusts or soil dusts, cannot be ignored (Deichmann and Radomski, 1968; Radomski and Deichmann, 1968; Roan, Laubscher, and Morgan, 1969; Davies, Edmundson, and Raffonelli, 1975). Because of nonvolatility, DDT and similar compounds are easily carried in dusts; further, inhalation may often be a more effective way of introducing a contaminant than strictly oral ingestion. Highly scattered values may cause one to suspect localized sources of contamination (Deichmann and MacDonald, 1971).

4.9.5 Isomers and Metabolites of DDT

At this point it is necessary to mention isomers and metabolites of DDT for understanding of the processes of absorption, metabolism, and excretion of the pesticides.

4.9.5.1 o,p-DDT — This is the chief isomer of DDT. Technical DDT is 60 to 75% p,p'-DDT; the remainder is o,p-DDT and other compounds. o,p-DDT may show some differences in effects from p,p'-DDT (see Sect. 4.9.8); however, its chemistry is otherwise very similar, and it gives derivatives similar to those of p,p'-DDT.

4.9.5.2 DDA — Bis(p-chlorophenyl) acetic acid (for the p,p'-derivative), or Dichloro Diphenyl Acetic acid. This is a metabolic oxidation product of DDT. It is the chief metabolite of DDT excreted in the urine, which is what would be expected from the water solubility conferred by the presence of the acid group.

Because of its polar nature, DDA may be separated from other DDT metabolites on ion exchange resin and analyzed separately (Cueto, Barnes, and Mattson, 1956). For separation by gas chromatography the methyl ester may be formed.

4.9.5.3. DDD (also called TDE) — 1,1-Dichloro-2,2-bis(p-chlorophenyl)ethane, or Dichloro Diphenyl Dichloroethane. This compound has one chlorine atom less (on the end carbon of the ethane moiety) than DDT, and is not necessarily a derivative of it but is a pesticide in its own right, having formerly been used on fruits and vegetables (Meister et al., 1977, p. D255); however, it can be formed from DDT by metabolic action.

4.9.5.4 DDE — 1,1-Dichloro-2,3-bis(chlorophenyl)ethene, or Dichloro Diphenyl dichloro Ethylene. This is formed from DDT by loss of one molecule of HCl, either chemically or by biological action. This results in a double bond or unsaturation between the two carbons of the ethane (now ethene) moiety. This compound is not an insecticide. On further dehydrochlorination plus oxidation, DDA is formed.

All of the above compounds may be indicators of exposure to DDT. The compounds may be analyzed for separately, and also "total DDT equivalent" may be given.

4.9.6 Fate of DDT; Absorption, Metabolism, and Excretion

In the national survey, of the total DDT equivalent found, 80% was DDE. Similarly, in 1964, Hoffman, Fishbein, and Andelman found DDE to be 75% of total DDT-derived material in human adipose tissue samples. In only 7 of 282 cases was the DDT level higher than that of DDE. The trend of DDE as a proportion of total DDT equivalent is up in the general population. This DDE is not appreciably derived from ingestion of DDT but rather by intake of DDE formed in the environment from DDT. The normal fate of DDT in the human body is to be either dechlorinated to DDD and then metabolized to the water-soluble and excretable DDA, or to be excreted directly as DDT. DDT goes into fat, but there is a slow equilibrium between fat and blood (see, for instance, Deichmann and MacDonald, 1971). Thus the DDT is not irreversibly stored — its excretability, in the words of Hayes (1965), is "intermediate between that of most drugs and that of lead and other bone seekers."

DDE, degraded in the environment by microbal action, is not easily excreted and thus builds up slowly in the fatty tissues. As studied by Morgan and Roan (1971), both the propensity for storage and stability, once stored, increase in the order p,p'-DDD $\leq$ o,p'-DDT < p,p'-DDT < p,p'-DDE. Thus it is critical to the fate of ingested DDT whether it is dechlorinated to DDD, in which case it is metabolized to DDA and excreted; or dehydrochlorinated to DDE, in which case it is stored; however, this latter reaction seems not to occur to any great extent in the body.

DDT ingested as such is partly absorbed and partly excreted in the feces. The absorption of DDT is facilitated by the presence of fats (Anon., 1962). DDT in oily solution can be absorbed through the skin. DDE is also partly absorbed and partly excreted in the feces. DDA in a conjugated form is found in the feces. Hoffman, Fishbein, and Andelman (1964) state that some DDE can be oxidized to DDA, which is conjugated in the liver, and the conjugates are excreted both in the bile and in the urine. Other metabolic products may also be found. DDE is presumably less toxic to humans than DDT (if one can extrapolate from animal testing to humans), and so the conversion of DDT to DDE can be considered a form of detoxication (Hoffman, Fishbein, and Andelman, 1964), albeit not a very efficient one.

Excretion of DDT in the urine is slight. In some cases, practically none is found (Vioque, Saez, and Albi, 1977), whereas in others only trace or small amounts may be present (Price, Young, and Dickinson, 1972). DDT is excreted in the feces in most animals, but not to any great extent in man (Hayes, 1975). Some DDT may be transformed by bacteria in the gut to products which are then absorbed and may be excreted in the urine, no longer as DDT (Morgan and Roan, 1972). Excretion patterns are slower in man than in the monkey, dog, and rat (Morgan and Roan, 1971), and loss of DDT from adipose storage is slower in man than in these and other animals.

4.9.6.1 Hair as Excretory Pathway — The role of hair and its associated lipids as an excretory pathway for chlorinated hydrocarbons, including DDT, was examined by Matthews, Domanski, and Guthrie (1976). It was found that excretion via hair could be a significant factor in eliminating chlorinated hydrocarbons which resist metabolism. A similar elimination may occur through skin sebaceous gland secretion.

4.9.6.2 Smokers and DDT — Smokers, even though exposed to an extra load of DDT and derivatives from residues on the tobacco, show no higher levels of these contaminants in their adipose tissue than do their nonsmoking compeers in the general population (Domanski et al., 1977). Smokers excrete more DDA than do nonsmokers. It would seem that microsomal oxidases are activated in smokers, to the extent that the added pesticide load is kept up with. On the other hand, the residues of dieldrin for the male smoking group, particularly black males, were found to be marginally greater than those for the nonsmoking groups and to reflect linearly the number of cigarettes smoked. The authors point out that the amount of dieldrin residues on tobacco is inconsequential compared with the intake from food, in contrast to the situation with DDT.

4.9.7 Distribution in Tissues

4.9.7.1 Distribution with Respect to Disease — As has been mentioned, DDT is stored in fatty tissues, but is in slow equilibrium there with blood (Deichmann and MacDonald, 1971). DDT may be mobilized by changes due to various illnesses. This is also true for other pesticides, as shown by the study of Casarett et al. (1968), who determined levels of DDT, DDD, DDE, dieldrin, and heptachlorepoxide in tissues from 44 autopsies with as many as 12 tissues from each autopsy set. Subjects with the highest total residues in the tissues were those with evidence of emaciation, carcinomas, and various pathological conditions of the liver. Levels in sudden-death subjects were clustered near the center of distribution, in contrast to those in subjects who had undergone prolonged periods of illness before death. It was considered that levels in the lungs and liver showed recently entered material, whereas adipose tissue levels showed storage. Pesticides in viscera are likely to be part of lipoid elements in parenchymal tissue and thus to be in a position to interfere in intralipoidal cycles and thus with function.

The authors make the point that wasting disease, hormone stress, and the metabolic perturbations of various diseases may cause a mobilization of stored pesticide material, with possible toxic effects. Similarly, release of PCBs and of p,p'-DDE into the blood of patients with severe wasting disease (carcinoma) has been noted by Hesselberg and Scherr (1974). Radomski et al. (1968) have also noted high levels of DDT and DDE in the blood of patients with carcinoma, but not in patients with primary brain or liver tumors. In the Hesselberg and Scherr study, the patients were too sick for nervous system symptoms such as circumoral paresthesias, malaise, skin sensitivity, tremor, and disturbances of equilibrium to be noted. In birds and lower mammals, however, obvious nervous symptoms and even death have been caused by release of stored pesticide residues.

4.9.7.2 DDT and the Fetus — DDT and DDE (and other organochlorine pesticides) cross the placenta and are found in fetuses. The levels in blood of premature babies are higher than in the blood of normal-term infants, likely explained by the lesser body fat of the premature infants (O'Leary et al., 1970). Stillbirths and abnormalities have not been found to be associated with high levels of DDT or DDE (Rappolt and Hale, 1968; Curley, Copeland, and Kimbrough. 1969; O'Leary et al., 1970).

DDT affects nervous tissue and also causes other disturbances of function. Admittedly, these results appear only over a long period of time. However, the fetus is particularly vulnerable because of the intense program of differentiation events taking place during gestation. Spyker (1975) has considered the impact of exposure to low levels of chemicals on development, including behavioral and latent effects. Effects of methyl mercury were used as an example. The author makes the point that there are compensatory mechanisms that initially may mask the effects of a contaminant, but as aging, repeated exposure to stress, cell death, and other effects on systems occur, the delayed effect of the early lesion may be manifested.

4.9.8 Effects of DDT

The effects of DDT are mainly manifested in the environment. Fish and other aquatic organisms concentrate DDT (Bevenue, 1976); animals can become sick from eating contaminated fish. Birds are particularly susceptible to DDT poisoning. They suffer hormone stress, and their calcium metabolism is affected, resulting in lowering of egg production and production of nonviable eggs, in addition to metabolic changes. In man, the effects of DDT are mainly on the nervous system (Schafer, 1968; WHO Scientific Group, 1975). However, the fact that DDT sequesters in relatively inert fat keeps it from exerting its full effect. Acute DDT poisoning results in vomiting, skin sensitization, eye irritation, and dizziness, but long-term, chronic effects are considerably more subtle, and at the declining levels which are now being reached, DDT is not considered to be a great hazard (Hayes, Dale, and Pirkle, 1971; Deichmann and MacDonald, 1971).

DDT, particularly o,p'-DDT, shows some effect on estrogenic systems, as studied by Nelson, Struck, and James (1978) in rats and with human tissue *in vitro*. Activity of estradiol was enhanced by treatment with o,p'-DDT; it was postulated that the o,p'-DDT may replace estradiol from nonspecific sites, making it more available for specific sites. In this connection, Schoor (1973) has studied the binding of p,p'-DDE to serum proteins. Release of the DDE could result in toxic or pharmacologic effects. Binding of the contaminant would protect it in some measure from degradation. Finally, Rashad et al. (1976) have studied the association between serum cholesterol and serum organochlorine residues in 3568 subjects. Results indicate that p,p'-DDE may stimulate synthesis of cholesterol in the liver, leading to an elevated serum cholesterol.

4.9.9 Load of DDT in the Environment

The decline in stored DDT and DDE noted in the national surveys is hopeful. Some effects may already be noted. For instance, Spitzer et al. (1978) have noted an increase in productivity of ospreys in the Connecticut—Long Island area, reflecting a decrease in environmental levels of DDT. The decline may be expected to continue, albeit at a slower rate, until the levels become asymptotic with the declining levels in the environment. This process is apt to take a considerable time. The estimate of production of persistent pesticides from 1950 to 1970 is 3000 million lb (Finlayson and MacCarthy, 1973). A good part of this was DDT, and the figure for the total production of DDT is of the order of 2 million metric tons (4400 million lb; Maddox, 1972). Woodwell in 1966 (cited in Niering, 1968) estimated that at that time there was 1000 million lb of DDT circulating in the biosphere. This is perhaps about half of that which had been produced up to that time. The levels and effects of this DDT (summation of DDT and its natural metabolites) at a succession of environmental and trophic levels are given by Goodman (1974). Taking 1 as the solubility of p,p'-DDT in water (this corresponds to 1 ng/g water, to the nearest factor of 10), total DDT levels in the biosphere cover nine orders of magnitude (in ng/g): from 0.01 in seawater, where the effect noted is blocking of the development of certain planktonic copepods; to 0.1 falling in rain; to 10, which is the WHO/FAO proposed acceptable daily intake for man/g body mass; to 100 in the fat of Waddell seals and of penguins in Antarctica; to 1000 in human fat in the U.K.; to 10,000 in human fat in the U.S. (this is an experimentally lethal concentration in the brains of many birds); to 1 million in the fat of adult pheasants, with some mortality and impaired chick survival (this same level has been found in the fat of ostensibly healthy U.S. workers formulating DDT for 20 years); to 10 million in the pectoral muscle of eagles found dead.

4.9.10 Analysis of DDT

Ruzicka (1973) distinguished five basic methods of analysis: (1) functional group analysis; examples: colorimetry, chemical reactions, (2) biological test methods, (3) chromatographic methods, (4) spectroscopic methods, (5) radiochemical methods. All of these have been used for DDT and other pesticides. Colorimetry was an early method; this has been superseded by gas chromatography. Some pitfalls and shortcomings of any of the methods of analysis have become evident with experience. Thus, when 34 soil samples dating back to 1909 to 1911 (long before the advent of organochlorine pesticides) were analyzed, 32 showed apparent insecticide residues. These were eventually attributed to certain interfering soil constituents (Frazier, Chesters, and Lee, 1970; cited in Edwards, 1973*b*). PCBs give a pattern of peaks on a gas-liquid chromatogram similar to those of dieldrin, DDT, DDE, aldrin, and heptachlorepoxide. Cleanup on a column of silicic acid removes this interference. Extraction of the pesticide from the tissue is often a problem. This question has been treated by Kadis, Jonasson, and Breitkreitz (1969) and by Mes and Campbell (1976). It was found by Dale, Miles, and Gaines (1970) that pretreatment of serum with formic acid improved the extraction of DDT and metabolites. Other investigators have also developed effective protocols for preparation of samples. Ecobichon and Saschenbrecker (1967) have noted dechlorination of DDT, even in frozen blood. Some estimation of loss of this kind may be needed. Contamination must also be guarded against. Atallah, Whitacre, and Polen (1977) have studied artifacts which arise in analysis of organochlorine pesticides in human adipose tissue, with particular reference to cyclodienes. Confirmatory techniques are needed to rule out false positives. For screening, extremely sophisticated methods may not be needed. Several authors (Klisenko and Yurkova, 1967; Gabica, Watson, and Benson, 1974; Coutselinis and Dimopoulos, 1971; Nachman et al., 1969) have presented simplified gas chromatographic methods, thin-layer chromatographic methods, and methods to distinguish between classes of pesticides. An interesting method is the one of Sadar, Kuan, and Guilbault (1970), which takes advantage of the fact that cholinesterases extracted from different sources are inhibited or not by various pesticides. Readout is by fluorescence of a fluorogenic substrate acted upon by the cholinesterase. The method can distinguish between chlorinated, organophosphorus, and carbamate pesticides. From time to time, recommended methods of analysis and recommendations for further work are given in the JAOAC (example: Corneliussen, 1976).

SECTION 5

ORGANOPHOSPHORUS, CARBAMATE, AND MISCELLANEOUS PESTICIDES

5.1 INTRODUCTION

As mentioned by Durham (1969) and other authors, the organophosphorus and carbamate insecticides are in general much less persistent in the environment and in the animal body than are the organochlorine ones. The notion of functional accumulation (Westermann, 1969) has been discussed (Sect. 2.1). The danger with organophosphorus and carbamate pesticides is in their effects and not in their storage. The effect is inhibition of cholinesterase and in general of enzymes having serine in their active site. Enzyme-substrate complex is formed, but transformation and release of product does not occur. Durham notes that the combination between the organophosphorus moiety and the cholinesterase is generally more stable than that between the carbamate molecule and the enzyme. In fact, as studied by Witter (1963), the carbamate-to-cholinesterase bond may be so labile as to cause difficulty in carrying out a meaningful test on blood from persons exposed to carbamates.

Because of their relatively nonpersistent character, we did not include body-burden data — and there are few data of this kind in the literature — for the organophosphorus and carbamate pesticides and for some organochlorine pesticides not discussed in Sect. 4, with some exceptions, in phase I of this report. Many of these pesticides are water soluble and thus tend to be fairly easily excreted in the urine. Sometimes they are esterified or otherwise modified to make them less water soluble; but here esterases would split off the modifying group, rendering them again water soluble, and further metabolism might also ensue. This is not to say that these pesticides are without danger, but the danger is more episodic than in the case of the more highly persistent pesticides. An example is poisoning from residues of paraquat used to spray crops and, in particular, marijuana. Paraquat is 1,1'-dimethyl-4,4'-bipyridinium ion, a heterocyclic compound, furnished as the dichloride salt, which is freely water soluble. According to the Pesticide Usage Survey, a total of 1,005,340 lb of paraquat was used in the U.S. in 1977, on a wide variety of field, nursery, orchard, and market crops. Episode summaries for reports involving a variety of pesticides are published regularly by the EPA Pesticide Episode Response Branch. Reports deal with specific pesticides, no matter what the source, or may deal with poisoning episodes of pesticides coming from a stated source, such as water (example: Report No. 63, 1976).

5.2 PRODUCTION AND USE

The Pesticide Usage Survey publishes use figures for more than 275 pesticides. Of these, 87 showed usage for 1977 of above 1 million lb. Among these were:

Alachlor: 2-chloro-2',6'-diethyl-N(methoxymethyl)-acetanilide, 54,389,601

Atrazine: 2-chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine, 76,244,343

Butylate: S-ethyl-diisobutylthiocarbamate, 28,499,799

Carbaryl: 1-naphthyl-N-methylcarbamate, 18,065,721

2,4-D: 2,4-dichlorophenoxyacetic acid, 26,661,972

Dichloropropene-Dichloropropane: 37,544,110

Linuron: 3-(3,4-dichlorophenyl)-1-methoxy-1-methyl urea, 12,863,516

Methyl parathion: 0,0-dimethyl-0-p-nitro-phenyl phosphorothioate, 63,418,309

MSMA: monosodium methanearsonate, 13,950,441

Propachlor: 2-chloro-N-isopropyl-acetanilide, 18,930,906

Elemental sulfur, over 70,000,000

Toxaphene: polychlorocamphene, 74,469,332

Trifluralin: *a,a,a*-trifluoro-2,6-dinitro-N,N-dipropyl-*p*-toluidine, 22,982,938

Total usage for the U.S. in 1977 of all pesticides listed is of the order of 900,000,000 lb. Perhaps the greatest use is for weed control — other uses are for control of root and stem and soil insects in cropland, for desiccation, for control of plant blight, for control of insects as such. The figures listed are for usage by major crop types and do not include figures for some other agricultural uses and for usage in the industrial and governmental sectors. We do not have estimates of the amounts of these other uses.

5.3 ENTRY INTO MAN. METABOLISM AND EFFECTS

Entry of these pesticides can come in food and water, in dusts, as residues on objects, and through the skin. Oudbier et al. (1974) have studied entry by the respiratory route during and following spraying, especially among pesticide workers. Cummings (1965) has presented a market basket report on pesticides in foods, following an earlier report. In the 1965 study, residues of the 2,4-D type of pesticide were found, whereas they had not been earlier. Kohli et al. (1974) have studied the absorption and excretion of 2,4-D in man. Because this compound is water soluble it is excreted in the urine. Tewari and Harpalani (1977) determined the distribution of 12 common organophosphorus pesticides in human autopsy tissues, following cases of poisoning. Levels were highest in the stomach, followed by liver and intestine, kidney, spleen, lung, heart, and brain, in that order. One would not necessarily find the same order in cases of chronic poisoning. As mentioned by Khokhol'kov and Burkatskaya (1964; cited in WHO Scientific Group, 1975), whereas analysis of blood tissues for a certain pesticide or its metabolite in the case of the organophosphorus pesticides may be of little value because of the high turnover of the compounds, the amount of ether-extractable organic phosphorus is indicative of exposure. Matsumura and Ward (1966; see also Matsumura, 1973) have studied the degradation of a number of organophosphorus pesticides by human and rat liver. Phosphatases, esterases, oxidases, conjugases, dealkylating enzymes, and dephosphorylating and dethiolating enzymes are active in processing the pesticide residues (above references and Anon., 1972). The nonpersistent pesticides appear in the milk and in the fetus, but to a lesser extent than the more lipophilic ones (Tolle et al., 1973).

Tocci et al. (1969) have studied the effects on enzymes of exposure to organophosphorus and other pesticides. Activity of alkaline phosphatase is increased. The pesticides affect cholinesterase activity and also interfere with metabolism at various points, for instance, at the level of glycerol-1-phosphate and with transaminase activity. Metcalf and Holmes (1969) have examined changes in EEG patterns and psychological, neurological, and biochemical changes in humans with organophosphorus exposure. There is an impact of organophosphorus compounds on the deep midbrain, as well as more superficially on the nervous system, as a slower response to exposure to these contaminants.

5.4 ANALYSIS

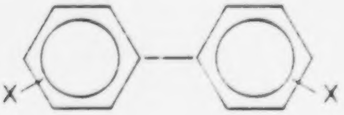
Analysis of these pesticides is by gas chromatography (Corneliussen, 1975), with a specific flame photometric detector being much used; by reversed-phase liquid chromatography (Askew, Ruzicka, and Wheals, 1969); by polarography coupled with liquid chromatography (Koen and Huber, 1970); by thin-layer chromatography (Tewari and Harpalani, 1977; Sherma, 1978; Paez and Farah, 1971); by testing of enzyme levels (Nicaise, 1970; Moeller and Rider, 1962); by a number of methods for specialized cases (Ruzicka, 1973); and by analysis of metabolites of the pesticides (Lores et al., 1978; Shafik and Enos, 1969; Hunter et al., 1972). Thin-layer chromatography is used to a considerably greater degree for analysis of these pesticides than is the case with the organochlorine ones, with quantitation by densitometry. Much greater use is also made of testing for metabolites. Kutz, Murphy, and Strassman (1978) have listed some chemicals detected in human urine and their pesticide origin. Thus, from carbaryl and naphthalene is found α-naphthol; from propoxur, isopropoxyphenol; from carbofuran, carbofuran phenol and 3-keto carbofuran; from malathion, the α-monocarboxylic and the dicarboxylic acid; from methyl and ethyl parathion, *p*-nitrophenol; from chloropyrifos, 3,5,6-trichloro-2-pyridinol; from organophosphorus insecticides containing the respective phosphate and phosphorothiosulfate groupings, dimethyl phosphate, diethyl phosphate, dimethyl and diethyl phosphorothionate, sulfates, and phosphorodithionates.

SECTION 6

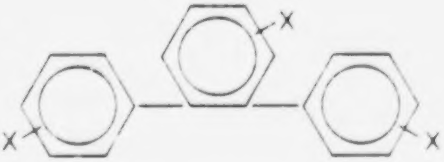
POLYCHLORINATED AND POLYBROMINATED BIPHENYLS AND TERPHENYLS

6.1 FORMULAS

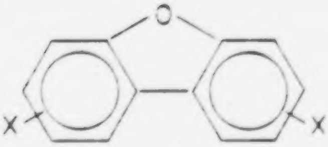
The formulas of chlorinated biphenyls, dibenzofurans, dibenzodioxins, and terphenyls (diphenyl benzene) are shown; X = chlorine atoms, indeterminate in number and position:



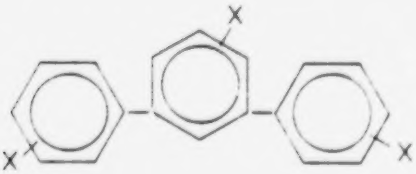
biphenyls



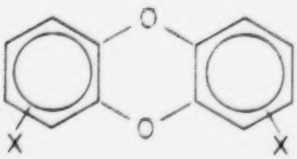
o-terphenyls



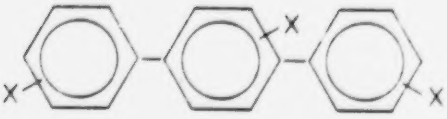
dibenzofurans



m-terphenyls



dibenzodioxins



p-terphenyls

The dibenzofurans and dibenzodioxins are produced by oxidation and condensation reactions in the manufacture of PCBs. They may also be produced by microbial action. See also section on PCP (Sect. 4.4); formation from condensation of chlorophenols. Given the ten possible sites of substitution, it is theoretically possible that 210 isomers and analogs could be found in a mixture of PCBs (Somers and Smith, 1971), plus others from the other compounds shown. Not all are present, but enough are to complicate reference to a standard in analysis.

6.2 POLYCHLORINATED BIPHENYLS

6.2.1 Production and Use

Somers and Smith (1971) estimate that production in the Western world at that time was about 100 million lb of PCBs annually, of which nearly 50% was being produced in the U.S. Kutz (1976) has given production figures for PCBs for the period 1930 to 1975. [PCBs were used as early as 1881 (Ouw, Simpson, and Siyali, 1976), but widespread use did not occur until the 1970s.] U.S. production for the period 1930 to 1975 was 1400 million lb, of which 150 million lb was exported. Three million lb was imported; U.S. sales were 1253 million lb, of which 758 million lb was currently in service, 55 had been destroyed, 290 was in landfills and dumps, and 150 was in soil, water, air, and sediments.

The PCBs are synthetic oils with special physical properties of electric insulation, heat transfer, high vapor pressure, and great durability, even at high temperatures. They have had manifold uses. Finklea et al. (1972) distinguish between "closed" and consumptive uses. By definition, residues from the consumptive uses get into the environment, and a goodly amount of PCBs from the "closed" uses also does, from accidents, deterioration, and eventual disposal. Kutz (1976) lists current uses, which are: in electrical transformers and capacitors, in recycled paper as a contaminant, and in investment castings (imported). Uses which have been discontinued include: heat transfer and hydraulic fluid, lubricant and in cutting oils, plasticizer, wax extender, pesticide extender, in adhesives, in inks, in sealant and caulking compounds, and as a paper coating. U.S. sales in 1975 were about 65,000 lb; export sales were about 33,000 lb.

6.2.2 PCBs in the Environment and in Man

The distribution of PCBs is similar to that of the other persistent chlorinated hydrocarbons and occurs largely through lipid-associated pathways. PCBs enter the environment through the consumptive uses mentioned, through leakage, through burning of refuse, etc. PCBs enter into aquatic and land food chains (and have deleterious effects on organisms in these milieux) and are found in feeds and foods (Khan, Rao, and Novak, 1976). The presence of PCBs in sewage sludges is of particular concern (U.S.

Department of Health, Education, and Welfare, 1976). PCBs ingested, inhaled, or absorbed through the skin are found in the blood (being transported therein) (Hammer et al., 1972); are stored in adipose tissue (Price and Welch, 1972; Kuroki and Masuda, 1977), the types of compounds stored reflecting both the mixture of PCBs before intake and metabolic conversions; are secreted in milk (Savage et al., 1973; Savage, 1976; Musial et al., 1974); and are excreted by hair follicles and sebaceous glands (Matthews, Domanski, and Guthrie, 1976).

6.2.2.1 Effects in the Environment and in Man — Peakall (1975) has considered the effects of PCBs in the environment. With added hazards from the very highly toxic polychlorinated dibenzofurans and dioxins mentioned previously, effects in the environment and on animals are similar to those of the chlorinated insecticides. In man, chronic exposure at levels such as may be encountered in the work place results in chloracne, skin and eye irritation, nausea, edema of the face and hands, and abdominal pain (Ouw, Simpson, and Siyali, 1976). PCBs are of concern because of their relatively high vapor pressure, leading to absorption following inhalation; further, their oily or sticky or resinous nature, depending on the degree of chlorination, results in a hazard of absorption through the skin — example: electricians' rash from PCB-containing wire coatings. The acute toxicity of PCBs is less than that of most organochlorine pesticides (Peakall, 1975); however, fatalities have occurred following poisoning with PCBs and with the similar chloronaphthalenes (Flinn and Jarvik, 1936). Pathological findings on autopsy were liver damage, fatty degeneration, necrosis, and cirrhosis. In the Yusho incident in Japan in 1968 (Kuratsune et al., 1972), over 1000 persons were poisoned by eating rice oil contaminated by leakage of PCBs from a heat exchanger device. Symptoms were blindness, chloracne, nausea, edema, skin cysts, vomiting with jaundice, and abdominal pain. Babies born of mothers affected with the PCBs had skin discoloration due to passage of the PCBs through the placenta. It is noteworthy that the contaminated rice oil contained a higher proportion of polychlorinated dibenzofurans than did the original PCB heat exchanger oil, and the suspicion is that these were formed in service by heating and air oxidation.

Calabrese and Sorenson (1977) have reviewed the metabolism and health effects of PCBs. In rabbits, glucuronide-conjugated PCBs were excreted in the urine. Glucuronides and sulfates were excreted in the urine and feces of dogs; and in humans, 65% of intravenously injected hydroxylated chlorinated biphenyl was excreted in the urine and 20% in feces. Enzymes in the liver are capable of hydroxylating PCBs. Storage of isomers differs, the more highly chlorinated ones generally being retained longer. General storage levels are highest in adipose tissue, followed by liver, blood, heart, kidney, and brain. Effects of PCBs are increased liver weight, fatty degeneration and necrosis, and increased activities of enzymes such as nitroreductase and aromatic hydroxylase. Vitamin A storage is decreased in rats. PCBs alter lipid metabolism and may perturb absorption of fat-soluble vitamins from the digestive tract. Carcinogenic and teratogenic effects caused by chlorinated dibenzofurans and chloronaphthalenes present as impurities in PCBs are a possibility. PCBs cause hormonal stress as evidenced by increased levels of corticosterone. Reproductive effects of

PCBs may reflect increased hydroxylation of progesterone and testosterone caused by increased activity of hydroxylating enzymes provoked or induced by PCB's. PCB's show an immunosuppressive effect. Calabrese and Sorenson give special attention to human high-risk groups and point out that children and embryos and fetuses tend to lack the liver microsomal enzymes, including oxidases, hydroxylases, and conjugases, that in older persons would be mobilized to detoxify absorbed PCBs, and are thus particularly susceptible to damage. Similarly, individuals with liver infections may be at risk above the general population with respect to substances such as PCBs.

6.2.3 Analysis

Analysis of PCBs has been by gas chromatography, with electron capture or microcoulometric detector (Yobs, 1972). Zobel (1975) achieved separation of PCBs from DDE and DDT isomers by silica-gel chromatography; the gas chromatograph was used for quantitation of the compounds in the separated fractions. On direct gas chromatography (e.g., extracts of human fat samples, Zobel, 1975), the very complexity of the pattern of peaks is indicative of PCBs. Mes and Campbell (1976) have discussed problems of sample treatment, and Biros and Walker (1970) have confirmed the identity of peaks separated by gas chromatography by mass spectrometry. A basic dehydrochlorination may be part of the treatment of PCB-containing samples to remove other chlorinated compounds, since PCBs resist this treatment. Patterns of analysis of samples of PCBs are given by Nisbet (1976), including samples from soils, water, commercial samples, tissues, etc.

6.3 POLYCHLORINATED TERPHENYLS

Polychlorinated terphenyls, as well as being a contaminant in PCBs were at one time made as such in the U.S. for use in metal casting and some other uses. This production has been discontinued. PCTs have been found in human tissue (Anon., 1978*b*; Doguchi, Fukano, and Ushio, 1974), following accumulation through food chains or other routes. Concentrations in human adipose tissue are in the range 0.1 to 2.1 ppm (Doguchi, Fukano, and Ushio, 1974).

6.4 POLYBROMINATED BIPHENYLS

A serious poisoning incident occurred in Michigan in 1973–74. Between 1 and 2 tons of a PBB mixture for flame protection — "Firemaster" — was mixed with an animal feed supplement, "Nutrimaster." Effects were seen first in cows and then in humans. The consequences of this incident have been reviewed by Humphrey and Hayner (1975), Meester and McCoy (1976), Kay (1977), and others. PBBs have a number of uses, similar to those of PCBs; the most common use is as a flame retardant. Wallen (1977), reporting on the PBB situation in New Jersey, states that production of PBBs between 1970 and 1976 was over 13 million lb. PBBs are very persistent, bioaccumulate, and may be five to ten times as toxic as PCBs (Wallen, 1977). In the New Jersey investigation, PBB residues were found in human hair, in fish and shellfish, plants, soil and water, and in vicinities of production and use of PBBs (for instance, near a plant using PBBs in manufacture of wire coating). Levels were as high as 4200 ppb in soil, 430,000 ppb in sediment near an outfall, 37,000 ppb in reeds, and 240 ppb in fish. Levels were in the low ppm range in hair, blood, milk, and adipose tissue samples from affected persons in Michigan.

SECTION 7

MISCELLANEOUS COMPOUNDS

Included in these compounds are food additives, drugs, antibiotics, plasticizers, volatile organics, and miscellaneous substances. Data on occurrence and levels of some of these appears in the phase I document.

A great number of substances to which people are exposed are absorbed by them and stay at least a time in their bodies. Our capability to avoid exposure to nonnatural substances decreases as more and more of them are presented to us. A listing of all substances, exposure to which results in a measurable body level, if not a lasting body burden, is beyond the scope of this report. The following list, however, will increase awareness of the number and types of substances to which humans are exposed:

Hewitt, 1975. "Clinical implication of the presence of drug residues in food" (Emphasis on antibiotics).

Kolata, 1978. "Behavioral teratology: Birth defects of the mind."

Oehme, 1973. "Significance of chemical residues in U.S. food-producing animals" (Antibiotics, therapeutic agents, heavy metals, pesticides).

Blum et al., 1978. "Children absorb Tris-BP flame retardant from sleepwear: Urine contains the mutagenic metabolite 2,3-dibromopropanol."

Jaeger and Rubin, 1973. "Extraction, localization, and metabolism of di-2-ethylhexyl phthalate from PVC plastic medical devices."

Ayres et al., 1973. "Health effects of exposures to high concentrations of automotive emissions" (Mainly carbon monoxide, but also consideration of nitrogen oxides, hydrocarbons, and oxidants).

Freeman et al., 1978. "Identification of nitric oxide (NO) in blood."

Dowty, Laseter, and Storer, 1976. "The transplacental migration and accumulation in blood of volatile organic constituents."

Knowles, 1974. "Breast milk: A source of more than nutrition for the neonate" (Pesticides, metals, drugs, anticoagulants).

Laseter and Dowty, 1977. "Association of biorefractories in drinking water and body burden in people" (Thirty-four volatile organic compounds of below 250 molecular weight).

Fry and Taves, 1974. "Maternal and fetal fluorometabolite concentrations after exposure to methoxyflurane" (Widely used fluorinated obstetrical analgesic and anesthetic).

And there are numerous others. Data on physical and chemical properties, sources, air and water pollution factors, and biological effects on microorganisms, plants, animals, and man for more than 1000 organic compounds may be found in the "Handbook of Environmental Data on Organic Chemicals," by Verschueren (1977).

The Council on Environmental Quality in 1971 (Finklea et al., 1972) presented candidates for concern as "hidden pollutants." These included metals, chlorinated naphthalenes, chlorinated aliphatics, brominated biphenyls (a crisis has already occurred; see Sect. 6.4), one or more of the several hundred fuel additives, optical brighteners, and unknown intermediates in the manufacture or disposal of synthetic organic chemicals.

SECTION 8

ASBESTOS

8.1 INTRODUCTION

The general term asbestos refers to a group of fibrous, serpentine (chrysotile), and amphibole (actinolite, amosite, anthophyllite, crocidolite, and tremolite) minerals with the properties of high tensile strength, poor heat conductance, and general resistance to chemical attack (Cralley et al., 1968). The amphiboles tend to be straight and splintery, while chrysotile is a more flexible, curved, and hollow fiber. Asbestos minerals occur commonly in soils and rocks, with the chrysotile form constituting over 90% of the total geologic asbestos (Shride, 1973). This predominance is further reflected in asbestos production, with 95% of that amount being the chrysotile form (Hueper, 1965). The use of asbestos by man has largely been a twentieth century phenomenon, with usage increasing over a thousandfold in sixty years (Gilson, 1965). The majority of this is in construction-related fields, where the asbestos is incorporated into cement, plastic products, siding shingles, roofing material, insulation, and other products (Hueper, 1965). However, it occurs in other nonconstruction products such as textiles and automobile parts, with over 3000 various uses (Rosato, 1959). The versatility of asbestos has prompted a meteoric rise in its production, with an increase from 500 tons worldwide in 1880 to 4,000,000 tons in 1967 (Selikoff et al., 1967). The majority of asbestos is mined in Canada and the U.S.S.R., but there are significant deposits in over twenty countries, including the United States. Thus, recently, asbestos has become a significant environmental pollutant on a worldwide basis.

8.2 SOURCES AND LEVELS OF ASBESTOS IN THE ENVIRONMENT

Routes of entry of asbestos into the environment fall into two broad categories — natural and human based. For both categories the routes of dispersal and transport are the same, namely, by air and by water. The sources vary, however. Natural sources are limited to rock outcrops containing asbestoid materials. These can contribute to environment levels by abrasion and weathering of exposed surfaces by air (Selikoff, Nicholson, and Langer, 1972) or by water (Stewart et al., 1976). Entry from these means tends to be minimal, especially when compared with human-promoted entry. Stewart et al. (1976) found many areas with no appreciable background levels of waterborne asbestos fibers. However, in areas where naturally exposed asbestos-containing rocks were common, the background levels were as high as 48 fibers per liter at high flows. Although no figures were found in the literature for natural airborne levels, the magnitude is inferred as "infinitesimal" when compared with human-promoted input (Selikoff, Nicholson, and Langer, 1972).

In the U.S., mining and milling operations account for the majority (85%) of human-promoted emissions of asbestos, while reprocessing (10%) and consumptive uses (5%) contribute only slightly to the total (Davis and Associates, 1970). In 1968, this amounted to 5088 metric tons for mining and milling emissions out of a total of 5967 metric tons emitted. However, since most mining and milling operations are located in rural areas with sparse population densities, the impact on humans is not proportionally as high as the emission rates would indicate. Environmental levels for airborne asbestos fibers range from 0.1 to 95 ng/m^3 for urban areas (U.S. Environmental Protection Agency, 1974), and from 11 to 8300 ng/m^3 for point sources (Heffelfinger, Melton, and Kiefer, 1972). Waterborne fiber concentrations also show a wide numerical variation, with values for final industrial effluents of from $<10^6$ to 10^{12} fibers per liter, and for finished processed urban water in areas of industrial or natural occurrence of asbestos of from 0.13×10^6 to 1[illegible] x 10^6 fibers per liter (Stewart et al., 1976). These figures illustrate the degree to which asbestos has permeated the environment. Once in the environment, asbestos fibers are very resistant to alteration or degradation. The fibers are rarely incorporated into the biotic sphere, since floral uptake is minimal and faunal intake is by accidental inhalation or ingestion. Also, no metabolic requirement for asbestos is known in either kingdom. In short, in an environmental sense, asbestos is not recycled, it is merely distributed.

8.3 ENTRY, STORAGE, AND EFFECTS IN HUMANS

The entry, storage, and effects of asbestos in humans is well documented for the primary exposure route, inhalation. Exposure by inhalation is not limited to occupational situations due to the wide distribution of asbestos particles and varied usages of asbestos-containing materials. The size and shape of the particles delimit the extent of fiber distribution in the tracheal system, with long fibers concentrated in respiratory bronchioles and alveolar ducts, while shorter fibers penetrate into the air sacs (Timbrell, Pooley, and Wagner, 1970). The majority of the inhaled fibers remain lodged in the interstitial areas of the lungs, with approximately 1% of these becoming coated with the ferruginous gel (Gaensler and Addington, 1969). Tissue concentrations of mineral fibers per gram of dry lung averaged 6.5×10^3 and 45.2×10^3 in surveys of nonoccupationally exposed persons in two cities (Gross et al., 1974*b*).

There are several primary effects found as a result of asbestos exposure, including asbestosis, pleural plaques, and several types of cancers. Asbestosis is a chronic pulmonary disease characterized by interstitial fibrosis and pleural lesions (Scott and Hodge, 1971). Prolonged exposure results in extreme distortion of lung tissue, making recognition of alveoli difficult and producing distortion in the bronchioles (Hinson et al., 1973). Asbestosis is usually a restrictive rather than an obstructive respiratory impairment. Pleural plaques are layers of hyalinized fibrin formed by slow proliferation of fibroblasts and fibrocytes in the collagenous connective tissue (Ulrich, 1971). The site of damage is thought to be largely related to mechanical factors such as expansion and abrasion (Roberts, 1971). The formation of cancerous lesions has been associated with asbestos exposure, but was masked until recently by the severity and lethality of the above effects. Lung cancers are found in about 25% of the exposures studied (Selikoff, Churg, and Hammond, 1965), with the majority being bronchial carcinomas (Selikoff, Churg, and Hammond, 1964; Selikoff, 1974; Roe, 1968). Mesotheliomas, rare primary tumors of serosa tissue, are found on the pleura and peritoneum as a result of asbestos exposure (Thomson, 1970). The formation of these tumors has been associated with the size of the fibers, with a greater carcinogenic risk when the fibers are <0.5 μm or >10 μm in length (International Agency for Research on Cancer, 1973). The most striking feature about exposure to asbestos is the delay time of 20 to 30 years from initial exposure to disease-symptom manifestation (Selikoff, Nicholson, and Langer, 1972).

Although inhalation is the primary entry route into human tissues, it is not the only route. Ingestion and dermal contact with fibers are alternate routes. Dermal contact is limited to subcutaneous piercing by the fibers, with subsequent development of nontoxic warts. The role and effects of ingestion are more uncertain. Some researchers using animal species have concluded that no uptake or penetration of fibers into the gut epithelium occurs (Webster, 1974; Gross, Hanley, Swinburne, Davis, and Greene, 1974; Davis, Bolton, and Garrett, 1974), while others (Pontefract, 1974; Cunningham and Pontefract, 1973) have reported the absorption of fibers from the gut and subsequent transport in the blood and lymph systems. These differing results may be due to the use of different test species and sizes of asbestos fibers. There is some epidemiological evidence relating asbestos ingestion with a higher incidence of gastrointestinal cancer (Merliss, 1971; Lumley, 1976; Selikoff, 1974), but few decisive experimental animal studies.

8.4 IMPACT OF ASBESTOS ON THE PUBLIC

The general impact of asbestos on the public is well documented. Epidemiological and demographic studies have been done for many areas of the United States, Europe, and Africa. In the U.S. the urban environment results in higher levels of asbestos in the lungs (Rosen, Melamed, and Savino, 1972), but even among the cities there is variation. In comparisons, residents of the smaller cities or of more rural areas have significantly lower levels of asbestos in their lungs — for example, Duluth less than New York (Auerbach et al., 1977), Charleston less than Pittsburgh (Gross, Harley, Davis, and Cralley, 1974), and a series of towns in England, each progressively less urban and having lower environmental asbestos concentrations than London (Oldham, 1973). It has also been demonstrated that asbestos-body frequency increases with age (Cauna, Totten, and Gross, 1965; Gordon and Rosen, 1976). The major factor is occupational exposure, which extends even to contact within families having only one asbestos worker. However, due to the wide use and long latency period, specific analysis of sources and exposure levels is a complex task and will require further study for more definitive statements. A pilot study along these lines is that of Selikoff and Hammond (1968). In this study, asbestos was taken as a model for particulates and penumoconiotic dusts in general, and community effects of nonoccupational environmental exposure to asbestos were noted.

8.5 ANALYSIS

The analysis for asbestos in tissues is primarily a microscopic investigation. The tissues (primarily lung) are prepared by either sectioning or chemical digestion (Rosen, Melamed, and Savino, 1972; Gordon and Rosen, 1976). The asbestos fibers or ferruginous bodies (fiber cores with iron-rich gel coating) are identifiable by either light, X-ray, or electron microscopic analysis (Langer et al., 1970; Gross et al., 1972). Some discussion has emerged on the variability of the fiber core in ferruginous bodies (Langer, Selikoff, and Sastre, 1971; Gross, Cralley, and deTreville, 1967; Gross, deTreville, and Haller, 1969), with conflicting evidence indicating that a majority of fibers can be either asbestos or nonasbestos. This uncertainty complicates the interpretation of cause-effect relationships in epidemiological studies. A bias inherent in the analysis technique is the use of light microscopy to select ferruginous bodies for electron microscope analysis. This preselecting method tends to overlook the smaller (<5 μm) bodies which are mainly asbestoid in nature due to the greater fragmentation rate of asbestos fibers as compared with fibers of other materials. The number of reported nonasbestos ferruginous cores (Langer et al., 1970, Langer, Selikoff, and Sastre, 1971) is thereby increased. In any case, the analysis is limited to microscopic techniques due to the lack of chemical degradation or metabolic by-products in the organism.

SECTION 9

THE HALOGENS: FLUORINE, CHLORINE, BROMINE, IODINE, AND ASTATINE

9.1 FLUORINE

9.1.1 Fluorine as Essential Element. Levels of Response to Fluorine (as Fluoride)

Fluorine is an essential element, albeit at a very low level of concentration. It is essential in the ppb range for nucleation of deposition of bone crystal (Newesley, 1961; Perdok, 1962; Brown, 1966) and at a somewhat higher level for maintenance of fertility and growth in animals (Messer, Armstrong, and Singer, 1974). It is a beneficial element at a middle level (the level of fluoride in the ocean is about 1 ppm, and this is the level that is optimal in drinking water for tooth and bone health — the levels in groundwaters and river waters are generally lower than this), and it is harmful at higher levels. Fluoride thus typifies the classic three levels of biological response to an element: a low-concentration plateau of essentiality, rising to another plateau of beneficial or pharmacological action, rising to a third plateau of overt deleterious effects.

9.1.2 Absorption and Excretion. Fluoride in Bone and Other Body Compartments

Absorption and excretion of fluoride are relatively passive. At optimum fluoride intake, a steady-state concentration is set up in the various body compartments. At higher intakes, there is a slow increase in bone fluoride concentration, with possible hypercalcification, development of bony spurs, and the like. Fluoride in the bone does not cause fluorosis; damage comes when fluoride is present in excess in the blood and interferes with the metabolism of osteocytes and osteoblasts (Hodge and Smith, 1968). The effect is seen in the teeth as mottling, when fluoride is present in excess during the period of tooth calcification. For bone the effect may occur at any time, resulting in hypomineralization at one place and hypermineralization at another. Calcification zones may occur in other organs also, for instance, the aorta. A proper level of fluoride intake may actually reduce unwanted organ calcification (Bernstein et al., 1966). The fetus uses fluoride and draws on the mother for it; in cases of excess fluoride the placenta may play a regulating role (Dean, 1936; Gedalia et al., 1964). Fluoride does not easily get into the brain (Armstrong et al., 1970), and some other compartments of the body are relatively protected or at least show slow dynamics with respect to changes in concentration of fluoride (Gedalia and Zipkin, 1973).

9.1.3 Fluoride in the Environment. Sources and Uses. Balance of Effects

Fluoride is widespread in the environment, having been introduced into the earth's crust along with phosphate rock by volcanic action in geologic time. Industrial introduction of fluoride may come by processing of phosphate deposits for fertilizer, also by use of fluorinated compounds. Fluorination of organics is a major use of fluorine, and fluorinated compounds, hydrogen fluoride, other fluorides, and fluorine itself may be released. Fluorine and fluorine compounds are used in obtention of aluminum, in the manufacture of steel, brick, tile, and glass, in the manufacture of pesticides, and in a number of other applications. Dusts and fumes are sources for some fluorine or fluoride intake, although water is the primary source, with foods contributing a smaller amount. The controversy over fluoride in drinking water reduces to the fact that fluoride should be added to drinking water where it is lacking and taken out where it is in excess (Conway, 1959). The damage of exposure to high fluoride is increased bone deposition, with the sequelae mentioned above. Fluoride at high doses affects various metabolic processes, and there is some evidence that high fluoride may be fetotoxic, but fluoride as it is present generally is not found to have deleterious metabolic effects nor to be teratogenic, mutagenic, nor to promote or cause cancer. Fluoride is an irritant poison, but claims of skin rash, metabolic disturbances, illnesses, etc., due to fluoride at environmentally encountered levels have not been substantiated (Rubini, 1969; Bronner, 1969).

9.1.4 Consumption of Fluorine. Exposure Limits

In industrial situations, fluoride is generally absorbed through inhalation. The TLV (threshold limit value) for fluoride as F, in air, is 2.5 mg/m^3; for fluorine gas it is 0.2 mg/m^3 (ACGIH, 1971). Consumption of fluorine is increasing, and projected demand for the year 2000 is 1.9 to 2.5 million metric tons (MacMillan, 1970). There is a natural fluoride cycle, and fluoride released by the use of this amount of the substance will mainly return to and be diluted by the environment, without particular deleterious effect. This does not mean that emission of fluorine-containing substances should not be controlled, since localized excessive concentrations may have adverse effects.

9.1.5 Analysis

Fluorine has probably been analyzed for by more methods than any other element mentioned in this report. Early analysis was by chemical treatment of fluorine-containing material and diffusion or steam distillation followed by titrimetry (Smith and Gardner, 1955) or reading of the light absorption of a colored complex of fluorine (Samachson, Slovik, and Sobel, 1957; Venkateswarlu and Sita, 1971). Linde (1959) analyzed for fluoride with a sensitivity of 0.1 μg/ml body fluid by potentiometric titration of fluoride following enzymic treatment of biological samples.

Fluorescence quenching of a morin-thorium indicator following diffusion of fluoride from acidified samples was used by Taves (1966). The specific-ion electrode (Singer and Armstrong, 1969; Shen and Taves, 1974; Hall et al., 1972) has been very convenient for measuring ionic fluoride in a variety of samples. Other methods which have been used, reflecting partly the analytical needs and partly the kinds of samples being handled, have been gas chromatography (Ruessel, 1970), nuclear magnetic resonance spectrometry (Guy, Taves, and Brey, 1975), spark-source mass spectrometry (Curzon and Losee, 1977), neutron activation analysis (Gills et al., 1974), and atomic absorption (Brudevold et al., 1975).

9.2 CHLORINE

Chlorine is an essential element in the form of NaCl in the blood, HCl in gastric juice, chloride ion in transmission of nerve impulses, etc. Elemental chlorine (Cl_2) has been used as an irritating, choking war gas. The TLV for chlorine used industrially is 1 ppm (about 3 mg/m^3) in ambient air. Emission of chlorine may result from use of chlorine bleach and chlorine in industrial processes. Addition of chlorine to water to oxidize pathogenic bacteria and other objectionable substances has been practiced for about 70 years, apparently without harm to humans. Lately a hazard has arisen from the production of organochlorine substances by action of chlorine on organics in the water. The solution would seem to be to restrict the entry of the organics into the water — it would be difficult to match the economy and effectiveness of chlorine for rendering water pathogen free and for eliminating off-odors and tastes. Use of activated carbon on a large scale has been suggested as a way of removing organics before chlorination (Morris, in Jolley et al., 1978). This, and methods of disinfection other than chlorination, and studies on the environmental impact and health effects of water chlorination are considered in the symposium volumes edited by Jolley (1978) and by Jolley, Gorchev, and Hamilton (1978).

Methods for analysis of chlorine and chlorine-containing compounds (chlorides, chloramines, chlorine dioxide, etc.) in water and wastewater are given in the handbook "Standard Methods for the Examination of Water and Wastewater" (American Public Health Association, 1975) and include argentometry and other titrations, amperometry, potentiometry, and a variety of colorimetric methods.

9.3 BROMINE

(Greek: bromos, stench). At room temperature bromine is a liquid, volatilizing to a heavy vapor with a disagreeable odor and a strong irritating effect. It is employed chiefly for preparation of bromine-containing compounds, such as medicinal bromides, bromides as intermediates in chemical synthesis, organobromines in gasoline for antiknock effect and lead scavenging, in fire-retardant and fumigation formulations, etc. The

TLV for gaseous bromine is 0.1 ppm (about 0.7 mg/m^3). Aside from industrial exposure, entry into man is chiefly in food, bromine being always present with chlorine (Bloch, Kaplan, and Schnerb, 1959). Bromide has been determined by colorimetry (Goodwin, 1971; Cabanis and Bonnemaire, 1970), by X-ray spectrometry (Gofman et al., 1964; Natelson, Sheid, and Leighton, 1962; Beyerman, 1961), by potentiometry (Bartels, Ritter, and Auer, 1969), by mass spectrometry (Losee, Cutress, and Brown, 1973), and by neutron activation (Sklavenitis and Comar, 1967; Obrusnik et al., 1972).

The biological half-life of bromide in the human is 10 to 12 days (Sklavenitis and Comar, 1967). Bromide is eliminated almost entirely in the urine. It is retained slightly by the kidney in preference to chloride (Bloch, Kaplan, and Schnerb, 1959). Bromine is found in all tissues and fluids, some of it in organic combination. Bromine does not seem to be a cause for concern, whether from effects or from any buildup in concentration. Underwood (1971, pp. 434-436) mentions, however, that human dietary intakes have increased in recent years in areas where organic bromides are used as fumigants for soils and stored grains and in motor fuels.

9.4 IODINE

Iodine, as part of the hormones triiodothyronine and tetraiodothyronine (thyroxine) and in similar compounds, is essential for growth in all animals (Underwood, 1971, pp. 281-322). Iodine at very high concentration can be toxic, but the margin of safety for this element is wide. Iodine is present in all body tissues and fluids, but is particularly concentrated in the thyroid gland. The next sink in order of importance is the skeleton. The chief source of iodine is food, where it occurs as iodide. Iodine is mainly excreted in the urine, with small amounts in feces and sweat. Iodine has been determined by neutron activation (Bowen, 1959; Heurtebise and Ross, 1971), by X-ray spectrometry (Gofman et al., 1964), by flame spectrometry (Gutsche and Herrmann, 1971), chemically (Krylova, 1967), colorimetrically (Mantel, 1971), and by mass spectrometry (Losee, Cutress, and Brown, 1973).

9.5 ASTATINE

The final halogen, astatine, is so rare as to be a chemical (radiological) curiosity. It has no stable isotopes. It was synthesized in 1940 by Corson et al. (Weast, 1976) by bombarding bismuth with alpha particles. The longest-lived isotope, ^{210}At, has a half-life of only 8.3 hr. Astatine-219, half-life 0.9 min, is reported to be present in uranium ores. Like iodine, astatine concentrates in the thyroid gland.

SECTION 10

LEAD

10.1 INTRODUCTION

10.1.1 Historical. Past and Present Sources of Exposure to Lead. Levels of Use

Lead has been known and used since ancient times, having been smelted along with silver since about 2500 B.C. (Christian, 1969). The Roman civilization was a great user of lead — the per capita consumption of lead in Roman Italy was 0.004 tons per year; in urban U.S. now it is 0.006 tons per year. Exposure to lead in Rome was chiefly through water, wine, and food, from the use of lead in water pipes, in solder, and in cooking utensils, whereas in America today the sources are more manifold. A chief source is particulates in the air from dusts and from fuel additive combustion, from lead-containing paints and colorings, and from other dissipative uses of lead. Leaching of lead from soft glazes on pottery was at one time a source of lead in foods; this is less common now. A diminishing source of lead is from residues of spraying with lead-containing pesticides, such as lead arsenate, these pesticides having been largely replaced with organic ones. One source of concentration of lead is sewage sludge. While this removes lead from the effluent, it may reintroduce lead into the environment when the sludge is applied in agriculture. Waldron (1975) estimated usage of lead in the world at 4 million tons per year, increasing at that time by about 3.5% per year. U.S. production from domestic ores in 1974 is given as 602,000 metric tons, with U.S. consumption of primary and secondary lead combined being 1.45 million metric tons (Bureau of Mines, 1975). Ryan (1973) and the Bureau of Mines (1975) give lead consumption in the U.S. by product. Listed are metal products, pigments, chemicals, and miscellaneous. The sum for 1974 was 1,599,427 tons. Some product uses are more apt than others to put lead into the environment. Thus, while storage batteries are the largest use of lead (772,000 metric tons in 1974), about half of this represents lead reclaimed from old batteries. In contrast, all of the lead in tetraethyl lead is released to the environment, and this is also true for lead-containing paints and other dissipative uses.

10.1.2 Point Sources. High Lead Areas

Some point sources of lead are of particular concern. Thus, Baker et al. (1977) did a nationwide survey of heavy-metal absorption in children living near primary copper, lead, and zinc smelters. Dusts from crushing operations and particulate fallout from the smelting operations were sources of the pollution. Other studies are by Yankel, von Lindern, and Walter (1977); Landrigan et al. (1976); Levine et al. (1976) (lead scrap smelter); and Roberts, Gizyn, and Hutchinson (1974). The effect of a smelter on agricultural conditions in the surrounding environment has been studied by Lagerwerff and Brower (1974). Lead dietary intake was 50% above normal, and lead levels were high in home produce, milk, and the blood of animals and humans. A recent National Science Foundation publication (Wixson, 1977) discusses a project for control of environmental pollution by lead and other heavy metals from industrial development in the new "lead belt" of southeastern Missouri. The project aims at developing cooperative efforts between industry, agencies, and universities to control environmental pollution, and all aspects of the question are addressed in the report. Various aspects of lead in automobile fuels have been treated in another NSF report (Boggess and Wixson, 1977).

10.2 LEAD IN MAN

10.2.1 Absorption, Excretion, and Metabolism

Most lead comes from the diet. Much of the lead ingested, however, is excreted in the feces. Exposure to lead varies; it has been calculated, however, that the average daily intake of lead by an adult is 300 μg from food and beverages (Barry and Mossman, 1970), and of this about 10% is absorbed (Kehoe, 1961a). Barltrop and Khoo (1975) have studied the influence of various nutritional factors on lead absorption in rats. Absorption was increased by high fat, low mineral, and low and high protein. Low fat, low fiber, high fiber, and low and high vitamin diets had no effects. Note, however, that Sorrell, Rosen, and Roginsky (1977) found a deficiency of vitamin D to be associated with high lead levels in blood of lead-burdened children. Lead inhibits absorption of calcium; conversely, calcium is protective to some extent against lead. Rabinowitz, Wetherill, and Kopple (1975) studied the absorption, storage, and excretion of lead in human volunteers maintained in a hospital metabolic unit for up to six months. The subjects were fed constant low-lead diets, supplemented with nonradioactive lead isotope tracers. The concentration of tracer and total lead in diet, feces, urine, blood, hair, nails, sweat, bile, gastric and pancreatic secretions, and bone were measured by mass spectrometry. By transferring these subjects to a room with filtered air (the air having been at about 2 μg/m^3) and observing the rate at which their blood level fell, it was determined that about 15 μg of lead per day was inspired, about half as much as originated in the diet. This confirms the danger of lead from airborne particulates. Golz (1973) has criticized the emphasis by the EPA on the health effects of airborne lead; however, there would seem to be no doubt of the importance of this source of intake. Much lead in the environment has arisen by airborne contamination. This is indicated by the presence of lead in the snow and ice layers of Greenland. In a figure given by Hall (1972), the lead content of Greenland snow layers, at about 0.001 μg/kg in 800 B.C., is seen to rise slowly to about three times that level by the start of the Industrial Revolution, then to go over 200 years to 0.08 μg/kg, and then to rise dramatically from 1930 on, following the introduction in the 1920s of lead alkyls as gasoline additives.

10.2.2 Body Distribution

Confirming studies by other authors, Rabinowitz, Wetherill, and Kopple (1975) showed bone as the chief sink of lead. Entry into bone is slow and turnover is also slow. Lead from bone may or may not be mobilized under stress, disease, etc., depending on a number of factors. Because of the mass of the skeleton, any mobilization is dangerous (Hall, 1972). At moderate levels of exposure, lead does not accumulate greatly (Kehoe, 1961*b*, 1964), but at levels that are now met in America, there is significant accumulation (Berman, 1966; Schroeder and Tipton, 1968; Wessel and Dominski, 1977). Lead in bone crystal is relatively passive; the critical organ in bone is the marrow because of the effect of lead on heme synthesis (Albert et al., 1973).

Blood is the next compartment, followed by soft tissue. At least 90% of the lead in blood is bound to the erythrocytes (Hernberg, 1972, in Albert et al., 1973); the plasma lead is probably the more biologically active (Rosen, Zarate-Salvador, and Trinidad, 1974). In any case, blood lead is a fairly good indicator of lead exposure; urine is less so because of fluctuation in renal handling due to metabolic factors (Albert et al., 1973). Hair and teeth are good indicators of chronic exposure. According to Kopito, Byers, and Shwachman (1967), hair concentrates more lead per unit weight than any other tissue or body fluid, including bone, blood, and urine.

In the study of Rabinowitz, Wetherill, and Kopple (1975), at a level of intake of lead of 16 ± 4 μg/day in air and about 30 μg/day in the diet (this is about 1/10 of what persons are generally exposed to), size of the pool, turnover time, and flows in and out were as follows: bone, 200 mg, 104 days, 7 μg/day in and 7 μg/day out; blood, 1.9 ± 0.1 mg, 36 ± 5 days, 33 ± 5 μg/day going to urine, 15 μg/day going to soft tissue, and 2 μg/day coming back; soft tissue, 0.6 mg, about 40 days, 12 μg/day to bile, hair, sweat, nails, and pancreatic and gastric secretions.

10.2.3 Body Burdens of Lead. Effects of Lead at Low Levels

Lead deficiency has never been shown, and in fact, lead seems to be at least potentially harmful at any concentration; more specifically, lead at concentrations well below what have been considered "normal" or "safe" may have subclinical effects, often of a nervous order (David et al., 1976; de la Burdé and Choate, 1972; Moore and Fleischman, 1975; Waldron, 1975). The total body burden of lead in precivilization humans has been estimated to have been about 2 mg (Patterson, 1965). Schroeder et al. (1961) have estimated the body burden of "standard man" to be of the order of 80 mg, and Browder, Joselow, and Louria (1973) cite figures of up to 200 mg in persons living in particularly polluted communities. Blood lead levels of up to 40 μg/ml have been considered "normal"; at blood levels of 80 to 100 μg/ml overt toxic symptoms appear. Waldron (1975) considers that the progressive increase in environmental lead levels has caused levels in man to "approach closer to the threshold of clinical poisoning than any other environmental chemical pollutants." As stated by Christian (1969), intoxication by lead can be suspected when one or more of the following are present: (1) history of pica, (2) X-ray evidence of radio-opaque material in the GI tract, (3) X-ray evidence of lead lines at the metaphyseal ends of the long bones, (4) elevated blood or urine level (one notes that the blood level is a more trustworthy index than the urine level), (5) central nervous system signs or symptoms, (6) vomiting or other gastrointestinal disturbances, (7) positive test for coproporphyrin III in the urine, (8) reducing substance in the urine, (9) anemia, and (10) basophilic stippling of red blood cells.

The subclinical effects of exposure to lead are mainly neurological. Thus, Seppäläinen et al. (1975) have shown altered conduction time and electromyographic abnormalities at "safe" levels of lead exposure. Behavioral disorders and impairment of hand-eye coordination were shown by Moore and Fleischmann (1975). Altered peripheral nerve conduction velocity in children (Feldman et al., 1973), association between low levels of lead and mental retardation (David et al., 1976), and an association between lead and hyperactivity (David, 1974) have been described. Similar findings have been reported by a number of authors (Cohen, Johnson, and Caparulo, 1976; Landrigan et al., 1975; Pueschel, 1974; and others). Lead may have delayed effects (de la Burdé and Choate, 1972). Lead is teratogenic (Waldron, 1975). Human placental transfer of lead begins as early as the 12th week of gestation (Barltrop, 1968). The danger of this in terms of embryotoxicity and possible later effects has been discussed by Carpenter (1974) and by Fahim, and Hall (1976).

Other effects of lead at low levels, noted in animals but which presumably could also apply to humans (Waldron, 1975) are: (1) enhanced susceptibility to infection through impairment by lead of phagocytic activity, sensitization to toxins, interference with mechanism of clearance of particulates in the lungs, and impairment of formation of antibodies; (2) impairment of reproductive activity; (3) teratogenic effects; and (4) inhibition of various enzymes.

10.2.4 Biochemical Indicators of Exposure to Lead. Screening for Exposure

Children are particularly at risk with respect to exposure to lead because of intense metabolism occurring in their growing and formative years. Lead exposure in these critical years may have sequelae later on. Lead affects porphyrin metabolism, and testing of perturbations of this can indicate exposure. Hammond (1969) has schematized the synthesis of heme from glycine and has indicated the points at which lead interferes. The rate-limiting step of the anemia of lead poisoning is probably at the level of insertion of iron into protoporphyrin IX to make heme (Rimington, cited in Hammond, 1969; the enzyme involved is ferrochelatase). As a result of this, protoporphyrins and precursors pile up, notably free blood protoporphyrin and urinary coproporphyrin and porphobilinogen (Gaultier et al., 1960). It must be noted that hemes or porphyrins are used elsewhere in the body besides in hemoglobin: in oxidative enzymes and the cytochrome electron carriers, in nerve tissues, and so on. Thus the effect of the lead is multiple. One key enzyme in the porphyrin synthesis pathway is delta-aminolevulinic acid dehydratase. Decrease in the activity of this enzyme is the most sensitive index of lead exposure known, and in the case of lead poisoning in infants, there is good correlation between inhibition of ALA-dehydratase and the clinical status of the patient (Hammond, 1969). Chisolm, Barrett. and Harrison, (1975); Hernberg et al. (1970); and Kuhnert, Erhard, and Kuhnert (1977) (with particular reference to mother and fetus) are some of the authors who have studied the effects of lead in heme synthesis and the hematologic picture as an index to the degree of exposure.

Roels et al. (1976) studied the impact of air pollution by lead on the heme biosynthetic pathway in school-age children and recommended that 25 μg lead/100 ml blood be regarded as the maximum biologically allowable concentration of lead in the blood of such children. Their dose-exposure curves indicate a sensitivity to lead of children $\geq$ women > men. This is reflected in the work place, where blood lead levels of 80 to 100 μg/100 ml may occur in older male workers without great effect, whereas women and younger workers show signs of disturbances at lower levels (Browder, Joselow, and Louria, 1973). For instance, encephalopathy due to lead poisoning occurs at lower blood lead levels in women than in men; however, this difference is not seen in children (Browder, Joselow, and Louria, 1973).

Determination of perturbation of porphyrin metabolism is highly useful in screening, but other indicators may also be used — blood lead levels, urinary levels, and hair. Behavioral and neurological indications have been mentioned. Barltrop and Killala (1967) examined the determination of lead in feces as an index of the ingestion of lead compounds and compared this with blood and urine measurements. Westerman et al. (1965) used the needle biopsy technique for determination of lead in bone marrow. Determination of lead in parotid secretions may be useful for screening (Browder, Joselow, and Louria, 1973); however, these levels tend to rise and fall erratically (Fung et al., 1975). Recently, Silbergeld and Chisolm (1976) showed increases in homovanillic acid and vanillyl mandelic acid in brain and urine of mice and in urine of children with increase of lead absorption, and suggested measurement of these catecholamine metabolites in the urine as a screening method.

10.3 ANALYSIS

The dithizone spectrophotometric technique using 5 or 10 ml of blood has been the standard wet chemical method for analysis of lead (King, Schaplowsky, and McCabe, 1972). In contrast, the free erythrocyte protoporphyrin test requires only 20 μl of blood (see, for instance, Piomelli et al., 1973; Chisolm et al., 1974). Metals other than lead form colored complexes with dithizone; all except thallium are eliminated in the procedure leading to the formation of the colored complex, and confusion with thallium is possible (Berman, 1966). Atomic absorption, which is a much used method, has been adapted to micro samples (Mitchell, Aldous, and Ryan, 1974; Posma et al., 1975), as has anodic stripping voltammetry (Anderson and Clark, 1974; Morrell and Giridhar, 1976). Proton-induced X-ray emission (Walter et al., 1974), X-ray fluorescence (Vaasjoki and Rantanen, 1975), emission spectrography (Niedermeier, Griggs, and Webb, 1974; Yoakum, Stewart, and Sterrett, 1975), and mass spectrometry (Barnes, Sappenfield, and Shields, 1969) are other methods which have been used. Based on the number of references, atomic absorption is apparently the most widely used method of analysis. We note that the dithizone method has recently been used as a screening method in the form of thin-layer chromatography of dithizonates (Beneitez-Palomeque, 1970; Baudot et al., 1976). More than one metal contaminant may be analyzed at a time. Mushak (1977) has considered problems arising in the analysis of toxic heavy elements having variable chemical forms, including arsenic, lead, and mercury. Sampling problems in the micro methods for lead have been discussed by Juselius, Lupovich, and Moriarty (1975), as well as procedures for avoiding such problems, and Khera and Wibberley (1976) have indicated proper procedures for ashing of tissue samples containing lead to avoid losses, with special attention to lead in the placenta.

10.4 NRC RECOMMENDATIONS

The Committee on Toxicology, Assembly of Life Sciences, National Research Council (Chisolm, 1976), has made several recommendations for the prevention of lead poisoning in children, which is the area of greatest concern. There are 9 recommendations; 6 of these deal with lead in paint, the greatest single source of lead intake for children. Recommendation 2 recommends 30 μg lead/100 ml blood as the level of concern, and recommendation 8 recommends more research in dose-exposure relationships in the 1- to 5-year age group. Recommendation 9 is a general one. Government agencies are urged to "... coordinate their policies regarding the limits for human exposure for industrial sources, consumer products, air, food, and water so that an individual's total exposure from various sources falls within a range which allows a margin of safety for those individuals in the population who are affected by relatively low doses."

SECTION 11

MERCURY

11.1 INTRODUCTION

Mercury is a dense, silvery, metallic element, occurring in liquid form at normal temperatures. It is relatively insoluble, and due to its high surface tension when dispersed breaks into many small droplets with increased surface area/volume ratios. This last property is important, since it increases the rate of vapor pressure equalization, resulting in the faster formation of vapor, the most toxic state of mercury. In the environment, mercury does not remain in its elemental form, but reacts or combines with other elements or organics. All of the combinations of mercury are in some way toxic, but the methylated (organic) and the chlorinated (inorganic) forms are the most toxic. Due to mercury's unique properties (for purposes of this document the term mercury will be used to represent all forms and compounds unless stated otherwise), it has found many uses in man's history. Major uses in industry include catalytic roles (in the formation of alkali and chlorine), electrical applications, as a constituent in paints and plastics, in processing wood pulp to paper, and in instrumentation controls (Gleason, Gosselin, and Hodge, 1957). Its toxicity makes it useful for pesticides and fungicides, especially when applied to grain (Frears, 1966), and it is used in some medicinal and dental preparations (Wallace et al., 1971; Bethea, 1936).

11.2 SOURCES AND PRODUCTION

The sources and production of mercury are primarily foreign, with only 4.7% of the ore of 0.005% mercury content located in the U.S. (U.S. Geological Survey, 1968). Thus the environmental sources of mercury pollution in the U.S. are primarily due to emissions from industry and manufactures, or dispersion in products. World production in 1975 was 9444 metric tons (Bauer, 1976), and U.S. consumption in that year was 1733 metric tons (U.S. Bureau of Mines, 1975).

11.3 ENTRY INTO THE ENVIRONMENT

Entry into the environment occurs primarily from waste or by-product sources. Until the dangers of mercury were realized, many industries, such as paper and chlorine-alkali producers, released inorganic mercury in wastewater or allowed escape through vaporization. Although such sources are controlled now, the downstream sites still act as reservoir sources for mercury (Nelson et al., 1971). In contrast to entry from industrial sources, product usage of mercury contributes little to the environmental burden due to the slow release rates. One major source not directly connected with any use of mercury is created by the burning of fossil fuels. Due to the high rate of fuel combustion in the U.S. it is estimated that approximately 1 million lb of mercury enter the environment (as vapor) every year (Nelson et al., 1971). As for total world atmospheric mercury levels, the estimate is 50 million lb (Krenkel, 1973). The majority of this estimate is based on natural release from soils and water through vaporization. Even with this large amount of atmospheric mercury, the concentrations are relatively low, levels ranging from 0.6 ng/m^3 (over open ocean) to 1200 ng/m^3 (over mercury deposits) (adapted from Fleischer, 1970). Urban areas tend to have higher air levels than do rural ones, as Jenne (1970) showed for Chicago and the surrounding countryside (4.8 vs 1.9 ng/m^3).

The level of mercury in natural water systems is much lower, ranging from less than 0.1 ppb to 17.0 ppb, with an average of 0.74 ppb (adapted from Wershaw, 1970). This is partly due to the low solubility of mercury, but primarily the low figures represent the conversion of inorganic mercury to organic methylated forms and their subsequent incorporation into the food chain or evaporation into the atmosphere. The transformation is accomplished by bacteria (such as *Methanobacterium omelanskii*) which occur in aerobic-anaerobic sediments, fish mucus and fish intestines, and prevent permanent sedimentation removal (Bisogni and Lawrence, 1975; Eyl, 1971; Jensen and Jernelov, 1969; Jernelov, 1973; Wallace et al., 1971). Methylation is facilitated by the presence of raw sewage. Both methyl and dimethyl compounds are created, with the volatile dimethyl entering the atmosphere or decomposing to methyl mercury, which is largely incorporated into the food chain (Wood, Kennedy, and Rosen, 1968). This bioconcentration is not necessarily stepwise through trophic concentration, but is also based on metabolic rate and food habits (Hannerz, 1968). The importance of this lies in the concentration of highly toxic methyl mercury in fish and subsequent ingestion by humans. No evidence was found for an essential metabolic role for mercury in any vertebrates or plants, so that concentration, degradation, and toxic effects are the only interactions mercury has with higher organisms.

11.4 ENTRY INTO MAN. TRANSPORT, DISTRIBUTION, AND EXCRETION

Mercury's route of entry into man depends on the chemical form encountered. Organic mercury enters readily by ingestion, dermal absorption, and inhalation, but human contact is most frequently by ingestion (Albert et al., 1973; Nelson et al., 1971; Nordberg and Skerfving, 1972; Yamaguchi et al., 1975). Inorganic mercury enters easily and most often through inhalation (Nelson et al., 1971; Nordberg and Skerfving, 1972), but can also be absorbed gastrointestinally, the rate of absorption in the latter case depending on the compound. Dermal entry of inorganics is often cited as a plausible route (Benning, 1958; Nordberg and Skerfving, 1972), but some investigators think that the rate is too slow to produce toxic effects (Nelson et al., 1971).

Once the mercury compounds have crossed epithelial barriers, transport is accomplished via the circulatory system. As with other heavy metals, mercury partitions between red blood cells, protein bodies, and plasma, with the ratios varying depending on the compound. The erythrocyte/plasma ratio for inorganic mercury is 2.5 (Miettinen, 1972), for elemental mercury is 1.0 (Lundgren, Swensson, and Ulfvarson, 1967), and for organic mercury compounds it is 0.1 to 0.2 (Birke et al., 1972). The binding preference of mercury compounds and, in particular, methyl compounds for erythrocytes is believed to be due to the affinity for sulfhydryl groups (Hughes, 1957; Goldwater, Ladd, and Jacobs, 1964; White and Rothstein, 1973). This is supported by the greater levels of sulfhydryl groups in hemoglobin (erythrocytes) as compared with plasma (Hughes, 1957; White and Rothstein, 1973). The binding of mercury to hemoglobin is not irreversible and will distribute based on chemical equilibria (White and Rothstein, 1973). Mercury levels in blood and their importance have been discussed in the literature, with some authors stating that there is a definite linear relationship between methyl mercury intake and blood-tissue levels (Skerfving, 1974), while others claim that methyl mercury intake is not linear with levels in tissues (Kevorkian et al., 1973). Perhaps the answer lies in the method of analysis (discussed later) or in the metabolic conversion of methyl mercury to inorganic forms by human tissues (Clarkson, 1972).

Absorption from blood to tissues is selective for inorganic mercury. The highest concentrations are generally found in the liver, kidney, and central nervous system (Bremner, 1974; Livingstone, 1971; Massaro, Yaffe, and Thomas, 1974). Methyl mercury also shows this concentration pattern, but tends to accumulate and remain to a greater degree in all tissues (Takeda et al., 1968). Kosta et al. (1974) showed evidence that the thyroid glands have the highest tissue levels of mercury, suggesting an affinity for iodine as the cause. Excretory function explains the high concentrations in the kidney and liver, but the concentration in the central nervous system may be due to the high lipid solubility and the short carbon chain of methyl mercury, which allow it to cross membranes easily (Bremner, 1974; Ellis and Fang, 1967). In the brain, mercury concentrates in the cerebellum and in particular in the gray matter (Glomski, Brody, and Pillay, 1971; Massaro, Yaffe, and Thomas, 1974), which may be due to mercury's affinity for the perikarya of nerve cells instead of their processes. In general, organic mercury remains longer in the system than does inorganic (Izumi et al., 1974), and in the tissues longer than in the plasma (Kurland et al., 1971).

Excretion of mercury is by the feces, urine, and bile. The major role is attributed to feces (Kurland et al., 1971) except for methyl mercury, where the bile is more important (Clarkson, 1971; Norseth and Clarkson, 1970). Excretion through the bile does not always eliminate the mercury, since some reabsorption occurs through the small intestine (Albert et al., 1973; Norseth and Clarkson, 1970). It is generally agreed that the amount in the urine is low and is not related to exposure level, duration, or poisoning symptoms (Jacobs, Ladd, and Goldwater, 1964; Kurland et al., 1971).

11.5 EFFECTS ON THE FETUS

The impact of mercury on the fetus is well documented. The fetus accumulates and concentrates mercury, in particular, methyl mercury, resulting in higher levels than in the mother. The accumulation is demonstrated by progressively higher mercury concentrations in the blood of the placenta, cord, and fetus (Baglan et al., 1974; Creason, Svendsgaard, Bumgarner, Pinkerton, and Hinners, 1976; Dennis and Fehr, 1975; Finklea et al., 1971; Mitani et al., 1976; Shinkawa, 1974). The result of this two- or threefold accumulation can be toxic effects evident in the fetus (e.g., growth retardation, brain hyperplasia, and lesion development), while no symptoms are shown by the mother (Koos and Longo, 1976). It has also been shown that there is a correlation between higher mercury levels in the fetus and suppression of the enzymes carnitine palmityltransferase, steroid sulfatase, and isocitric dehydrogenase (Karp and Robertson, 1977). The sensitivity of the fetus to mercury and its placental concentration is of the same order as for other nonessential or toxic trace metals.

11.6 GENERAL EFFECTS

The toxic or symptomatic effects of mercury poisoning are mainly related to its effect on the CNS. In this regard, poisoning by methyl mercury and the organic forms in general shows more effects and symptoms, than do inorganic forms due to stronger affinity for the CNS. The symptoms from methyl mercury poisoning usually include paresthesias of the extremities, mouth, lips, and tongue; unsteadiness of gait; loss of coordination; fatigue; irritability and rapid emotional changes; reflex changes; loss of hearing; concentric constriction of the visual field; gastrointestinal disruptions such as cramps, diarrhea, and vomiting; and in severe cases, paralysis or death (Benning, 1958; Eyl, 1971; Nelson et al., 1971). Poisoning due to inorganic mercury results in the same type of effects. Ingestion of inorganic mercury may cause additional effects in the intestines, liver, and kidney such as proteinuria and intestinal necrosis (Bremner, 1974). Other toxic effects attributed to mercury poisoning include chromosome breakage (Skerfving, Hansson, and Lindsten, 1970), disruption of mitosis spindle fibers (D'Itri, 1972; Ramel, 1969), and a possible association with amyotrophic lateral sclerosis (Currier and Haerer, 1968).

As a toxic substance, mercury acts on cellular and subcellular groups, especially on any entity with a sulfhydryl group. By tying up these groups, mercury can block membrane transport or alter selective permeability, thus leading to toxic consequences (Clarkson, 1972; Vallee and Ulmer, 1972). In particular, CNS effects can be traced to a cerebellar cortical atrophy (involving the granular cell layer of the neocerebellum) and to a cortical atrophy of the calcarine fissure-visual cortical area of the occipital lobe (Hunter and Russell, 1954). If the dosage is heavy, or chronic exposure extended, most of the cellular effects and symptoms are irreversible, and due to their delayed nature, quite undetectable until extensive damage is done (Nelson et al., 1971).

Thus, to control the toxic effects of mercury, prevention or limitation of exposure is the only viable preventive or therapeutic measure.

11.7 DEMOGRAPHY

Demographic studies of mercury's effects indicate the complexity of studies involving humans. Studies can be found in the literature that give opposite results on several factors, despite worldwide coverage. Most studies conclude that few absolutes can be identified due to the difficulty of connecting the result with exposure to mercury. The best documented and the most statistically significant trends associated with mercury exposure are increased tissue levels with age (Eads and Lambdin, 1973; Livingstone, 1971), greater risk in urban environments (Chattopadhyay and Jervis, 1974; Gowdy et al., 1977; Hecker et al., 1974), different levels between sexes (Creason et al., 1975), and increased risk with high seafood intake (Galster, 1976; Yamaguchi et al., 1975). Even these trends are disputed by some authors, pointing again to the difficulties in analyzing for mercury and interpreting results in spite of the large number of studies in this area. Many epidemiological studies have been done, particularly in response to mass poisoning by ingestion of contaminated foods. These include studies of poisoned fish (Bakir et al., 1973; Harada, 1968; Irukayama et al., 1965; Takeuchi, 1968, 1972), treated grains (Haq, 1963; Jalili and Abbasi, 1961; Ordonez et al., 1966), and contaminated pork (Likosky et al., 1970). All of these studies indicate how effective epidemiology has been in the recognition of mercury as a human hazard.

11.8 ANALYSIS

The methods employed in the analysis of mercury are determined primarily by the compound form. No one method has been found that can positively identify both organic and inorganic mercury. For this reason, there are currently several accepted procedures for mercury identification. For organic mercury the prevailing method is to use gas chromatography to separate the compounds, combined with a detection method such as electron-capture microwave emission spectrometry or mass spectrometry (Andelman, 1971; Baughman et al., 1973; Talmi, 1974; Webb et al., 1973). These methods are all variations of the Westoo (1968) procedure. They are characterized by a sensitivity of ±10%, applicability to biological and sludge material, and the ability to identify both concentrations and species (Nelson et al., 1971; Wallace et al., 1971), but are somewhat lengthy and expensive. Cappon and Smith (1978) describe a procedural variation that modifies the time and cost factors.

For inorganic and total mercury analysis, cold-vapor atomic absorption and neutron activation are the recommended techniques (Giovanoli-Jakubczak et al., 1974; Nelson et al., 1971; Wallace et al., 1971). Both are applicable to all materials, accurate, and rapid, but neutron activation is generally more precise (±2% vs ±20%) and more expensive (Jepsen, 1973; Westermark, 1972). Atomic absorption can be set up so as to give total, inorganic, and organic (by subtraction) concentrations (Giovanoli-Jakubczak et al., 1974; Magos and Clarkson, 1972). Other methods infrequently used for inorganic analyses are X-ray fluorescence (Anon., 1969; Boiteau et al., 1971), spark-source mass spectrometry (Alvarez, 1974), atomic-fluorescence spectrometry (Subber, Fihn, and West, 1974), and extraction by dithizone with colorimetric or spectrophotometric identification (Goldberg and Clarke, 1970; Gray, 1952). All of these methods are used less often, either due to less precise results, more costly equipment, limited applicability, or incomplete technology. However, with adequate development, some have potential for wider use.

All methods of mercury analysis must overcome the similar problems of background mercury contamination, loss by vaporization, and interference by other substances. Studies have shown that mercury concentration determinations vary widely among laboratories (Kaiser, 1973; Kevorkian et al., 1972; Rottschafer, Jones, and Mark, 1971) due to these common errors. Only careful work will eliminate these errors in results (Alvarez, 1974). As with the understanding of the mercury problem as a whole, the analysis techniques are improving rapidly due to research in the whole area of mercury and its potential hazards for man.

SECTION 12

ZINC AND CADMIUM

12.1 ZINC

12.1.1 Production and Use

Zinc is a soft metal that is an essential element with few toxic effects. It is used in many industrial processes, most prominently in galvanizing, die casting, and certain alloy combinations, with some agricultural and medicinal usage. United States production of zinc has increased from 556,247 metric tons in 1935 to 1,752,612 metric tons in 1973 (McMahon et al., 1974). This high rate of zinc use indicates how common a metal it is in the earth's crust and in man's society. Henkin et al. (National Research Council, 1978) give a continental crustal average of 70 ppm, ranking zinc twenty fourth in chemical element abundance and fourth in industrial metal use. This document reviews zinc production, use, environmental influence, analysis techniques, and toxicity.

12.1.2 Entry into the Environment

Zinc enters the environment primarily from mining, milling, and smelting operations. Release is also promoted by processing of other ores, especially copper and lead. Although some input is airborne, the majority is funneled by waste streams, including urban sewage, into aquatic systems. The levels vary from a low of 0.1 mg/l for nonmining streams to 21.0 mg/l for streams in mined areas (Mink, Williams, and Wallace, 1970). Urban sewage ranges from 0.01 to 61.7 ppm (Blakeslee, 1973). This is particularly important considering the sensitivity of fish populations to zinc levels. Zinc also enters the biotic sphere through absorption and uptake by plant species. As an essential element, it is retained and utilized in both plants and animals, including man. Zinc is not concentrated in most organisms when in usable forms, so food-chain accumulation is not a problem. Due to this lack of trophic concentration, human exposure potential is essentially the same as for other animals. Their intake levels are in turn controlled by exposure to contamination sources and the inherent soil levels (Dorn and Phillips, 1973). Therefore, these factors are the primary controllers of human interaction with zinc.

12.1.3 Zinc in Man. Absorption, Metabolism, Distribution, and Excretion

Zinc typically interacts with humans as an essential element. This is basically because internal control mechanisms enable the body to maintain minimum zinc tissue levels if sufficient environmental levels are present (Liebscher and Smith, 1968). The primary route of entry for zinc into the body is through the gastrointestinal tract, but occasionally entry occurs by dermal or tracheal means. Theoretically, active transport across barriers is accomplished by a tetrahedral, quadridentate ligand-organic molecule formed by a zinc-protein complex in the intestinal tract (Matrone, 1974; Suso and Edwards, 1971*a*,*b*). Passive transport has also been suggested (Saltman and Boroughs, 1960), but there is disagreement on this (Reinhold et al., 1973). Transport in the body occurs via the blood; the level of zinc is three to ten times higher in the red blood cells than in plasma (Herring et al., 1960). Zinc is distributed fairly uniformly throughout the body, with concentrations in bone, muscle, kidney, liver, and glandular tissues (National Research Council, 1978; Tipton and Cook, 1963). Excretion is primarily by fecal means (87%), with dermal loss (11%) of some importance (Schraer and Calloway, 1974; Tipton, Stewart, and Dickson, 1969).

The metabolic role of zinc is quite diverse. It functions in all parts of the body due to its incorporation in many enzymes. Zinc has been well established as a primary constituent in metalloenzymes, including carboxypeptidase A and B (Folk, 1971; Hartsuck and Lipscomb, 1971), thermolysin (Matthews et al., 1972), carbonic anhydrase (Lindskog et al., 1971), leucine aminopeptidase (Himmelhoch, 1969), alkaline phosphatase (Reid and Wilson, 1971), and alcohol dehydrogenase (Keleti, 1970). Zinc also promotes activity by other mechanisms such as the promotion-feedback-control functions of the hormones in the endocrine system (National Research Council, 1978). Other functions in which zinc plays a major role are membrane stabilization (Chvapil, 1973), muscle contractility (Cann, 1964), taste functions (Henkin et al., 1975), olfaction (Henkin et al., 1975, 1976), and visual functions (Vallee and Altschule, 1949; Williams, Foy, and Benson, 1975).

12.1.4 Toxic Effects

Toxic or deleterious effects of zinc are limited. Acute inhalation exposure to the fumes of heated zinc results in a short-term respiratory infection known as metal-fume fever (Hunter, 1969). Exposure produces fever, chest and leg pains, and general weakness. The victims usually recover in forty-eight hours with little or no long-term effects. The mode of action is unexplained (McCord, 1960). High plasma or tissue levels of zinc have been correlated with several diseases and cancers, but their role is uncertain. Breast cancer, osteogenic sarcoma, liver cancer, and bronchial cancer have all been correlated with high zinc levels (Fisher et al., 1976; Fisher and Shifrine, 1977; Janes, McCall, and Elveback, 1972; Morgan, 1970; Santoliquido, Southwick, and Olwin, 1976), while other researchers have found normal or lowered zinc levels associated with these diseases (Hirst et al., 1973; Koch, Smith, and McNelly, 1957). The contradictions may be due to the cancer location (high cancer levels found in tissues normally high in zinc content and vice versa) or to the type of cancer diagnosed (Addink and Frank, 1959; Olson, Heggen, and Edwards, 1958). For instance, tumors may occur in a region high or low in zinc without a causal relationship, or zinc may be released from damaged malignant cells, or zinc levels may be distorted by growth associated with the tumor (Mulay et al., 1971; Olson, Heggen, and Edwards, 1958). This same pattern of conflicting studies has been the case for noncancerous diseases such as pneumonia, hypertension, alcoholic cirrhosis, and atherosclerotic heart disease (Halsted and Smith, 1970; Marks et al., 1972; McBean et al., 1972; Netsky et al., 1969). The toxicity of zinc to humans may ultimately be traced more to cadmium impurities than to the zinc itself (Schroeder et al., 1967).

12.1.5 Zinc Deficiency. Balance of Zinc

Zinc deficiency in humans is well documented. Causes for deficiency can be traced to low levels in the diet and/or a "conditioned deficiency" based on cofactor or secondary condition interference affecting uptake (Vallee, Fluharty, and Gibson, 1947). The latter situation can be diagnosed by low levels of zinc in plasma and high urinary output of zinc. The initial results of low zinc levels are anorexia, smell or taste dysfunction, and mental and cerebellar dysfunction (Henkin et al., 1975). Prolonged deficiency can lead to growth reduction or retardation, impaired wound healing, and impairment of sensory perceptions (Burch, Hahn, and Sullivan, 1975). The importance of zinc in the diet is further supported by analysis of fetal or placental material. Levels of zinc in these tissues are normally equal to or higher than adult tissue levels (Baumslag et al., 1974; Creason, Svendsgaard, Bumgarner, Pinkerton, and Hinners, 1976). Furthermore, in areas with low zinc levels, there is a corresponding increase in birth defects. Rat teratology studies show the same trend. This circumstantial evidence indicates the importance of zinc for normal fetal development (Hurley and Swenerton, 1966; Sever and Emanuel, 1973). Thus it is usually the lack of zinc rather than an excess that is harmful to humans.

12.1.6 Demography

Demographic studies of zinc levels have found few definite causal factors for variance. Due to the various analytic techniques used and the different organs that were analyzed, conflicting evidence abounds in the literature. Contradictory correlations exist between zinc levels and sex (Hambidge et al., 1976; Klevay, 1974) and zinc levels in urban vs rural location (Creason, Hammer, Colucci, Priester, and Davis, 1976). No correlation has been found between levels of zinc and race, occupation, or pregnancy. There does seem to be a correlation with age, zinc concentration usually increasing till maturity at least. The increase or decrease in levels for adults depends on the tissues examined (Bala et al., 1969; Dubina, 1964; Petering, Yeager, and Witherup, 1971). Low income and low education can also be identified as factors in low zinc levels due to the generally poor diet of persons in these groups (Creason, Hammer, Colucci, Priester, and Davis, 1976; Hambidge et al., 1976). All of the general trends mentioned are affected by a wide random variation with geographic location. This indicates that zinc levels cannot be traced to one factor, whether it is occupational exposure, diet, age, or socioeconomic.

12.1.7 Analysis

There are many analytic methods employed in zinc determinations, with choice usually based on sensitivity desired, cost, or availability of equipment. Atomic absorption is the most widely accepted method due to high accuracy and great sensitivity (Hammer et al., 1971; Henkin, Mueller, and Wolf, 1975; Tipton and Stewart, 1969). There are many modifications to this technique, primarily aimed at reducing interference or sample handling time (Evenson and Anderson, 1975; Falchuk, Evenson, and Vallee, 1974; Henkin, 1971; Brudevold et al., 1975; Reinhold, Pascoe, and Kfoury, 1968). Neutron activation is also used when equipment is available due to its high sensitivity (Halvorsen and Steinnes, 1975; Henzler et al., 1974; Koch, Smith, and McNelly, 1957). This technique is preferred if multiple-element analysis is needed. Another multi-element technique is emission spectrography. Despite recent advances in excitation sources, the use of emission spectrography is declining due to lack of precise quantitative results (Fassel and Knisely, 1974*a*,*b*; National Research Council, 1978; Tipton and Cook, 1963). Other techniques infrequently used for zinc analysis include anodic stripping voltammetry (Williams, Foy, and Benson, 1975), electron microscopy (Carroll, Mulhern, and O'Brien, 1971), oscillopolarography (Shcherbak, Shcherbakova, and Marinets, 1975), and fluorometry (Mahanand and Houck, 1968).

In analyzing zinc in human tissues, one cannot overlook its association with cadmium. Cadmium and zinc are found together in soils, water, and plants. Any processing or concentration of zinc also results in a concentration of cadmium. This is due to their physicochemical similarity (Schroeder et al., 1967). In many ways their transport and storage are also similar, but the primary biological difference is that zinc is essential and cadmium is not. In terms of interaction, cadmium's effects predominate; for example, binding with thiol groups of enzymes favors cadmium due to its stronger affinities for sulfur. This means that it takes very little cadmium to disrupt the normal functions of zinc. Thus, when trying to understand the role of zinc in humans, cadmium interference and its toxic effects must also be considered.

12.2 CADMIUM

12.2.1 Production and Use

Cadmium is a nonessential metal, slightly softer than zinc with definite toxic effects. Unlike zinc, it is rare; ranking about 80th in crustal element abundance with an average of 0.15 ppm (Page and Bingham, 1973). Despite its relative rarity, cadmium poses a problem due to its association with zinc, copper, and lead ores; zinc in particular, since cadmium content increases as zinc content increases (Page and Bingham, 1973). Production of cadmium is totally based on extraction with other ores and has increased on a worldwide basis from 100 kg in 1870 to 14,058 metric tons in 1968 (Chizhikov, 1966). The recent increase is even more dramatic, with approximately 70% of the total cadmium production occurring in the last 20 years (Page and Bingham, 1973). Cadmium is used primarily for electroplating over iron, steel, or copper (45%); pigment and chemical uses (38%); alloy and solder formation (4%); and a variety of lesser needs such as batteries, fungicides, and phosphors (13%) (Page and Bingham, 1973).

12.2.2 Cadmium in the Environment

Generally, the levels of cadmium in air, soils, and water originate from natural sources. Cadmium is released into the active biosphere by man primarily through the mining and processing steps associated with the ore production, although some originates from product use and decay. In these respects, cadmium closely parallels zinc. The levels are normally low except near emission sites. Water levels of unpolluted locales range from 1 to 120 µg/l with a mean near 7 µg/l (Kopp and Kroner, 1970), while streams near emission sites can have as much as 3200 (Lieber and Welsch, 1954) or 4130 µg/l (Yamagata and Shigematsu, 1970). Air levels range from 0.001 to 0.350 µg/m^3 (U.S. Department of Health, Education, and Welfare, 1966) with urban or point-source localities having the higher values. Cadmium does have a cycle in the environment with plant uptake and animal concentration (Hammons et al., 1978). However, as with zinc, the factors controlling the levels are contamination exposure and inherent soil, water, and air concentrations.

12.2.3 Human Exposure to Cadmium

For the general population, exposure occurs primarily through ingestion of food (Hammons et al., 1978). Fish, meat, and some grains are prime sources of ingestible cadmium for man (Schroeder and Balassa, 1961). In occupational situations, inhalation of cadmium fumes can be a problem, especially if the presence of cadmium is unsuspected. Due to the high cadmium content in tobacco, smoking can also be a major route of exposure. The normal daily U.S. intake of cadmium is approximately 30 to 50 µg (Duggan and Corneliussen, 1972; Drury and Hammons, 1979).

12.2.4 Absorption, Excretion, Transport, and Storage

Following inhalation exposure, the absorption rate into the body depends on the particle size of the cadmium. Usually, 10 to 50% of the fume is taken into the body (Hammons et al., 1978), and the remainder is mechanically removed or isolated. Absorption from inhaled cigarette smoke is about 20 to 40%, resulting in 0.75 to 3.0 µg of cadmium absorbed per pack of cigarettes (Lewis et al., 1972). Absorption from ingested cadmium is much lower — on the average of 6% (Rahola, Aaran, and Miettinen, 1972). However, due to the greater frequency of cadmium in foods than in air, ingestion remains the principal route of entry. Once absorbed, transport is by the blood, primarily in the plasma. There is some binding to protein and red blood cells with time, but these are long-term equilibria and not strictly for transportation. Cadmium taken into the body tends to accumulate in tissues for long time periods. The half-life time is 20 to 50 years (Elinder et al., 1976), with an average of about 30 years (Friberg et al., 1974; Kjellström, 1971). This infers a progressive accumulation and a slow or nonexistent turnover rate; animal studies support this conclusion (Cotzias, Borg, and Selleck, 1961). Body storage is primarily in the liver and kidneys — often as much as 50% of the total body burden (Friberg et al., 1974; Nordberg, 1972; Tipton and Cook, 1963). Liver and kidney storage is based on a preferential binding of cadmium by a metallothionein type of protein which is in higher concentrations in these tissues (Livingstone, 1971; Oleru, 1976; Syversen, 1975). Excretion of cadmium is primarily by urine, with some loss by feces. The urinary output ranges from 1 to 2 μg/day (Friberg et al., 1974; Suzuki and Taguchi, 1970). Whether this output is tied to body burden or intake is uncertain, since studies have shown conflicting results (Adams, Harrison, and Scott, 1969; Piscator, 1973). Fecal excretion is very reduced, with levels of less than 0.1% excreted per day (Rahola, Aaran, and Miettinen, 1972). This small amount may originate in the bile, since cadmium has been determined there in minute traces (Smith, Kench, and Lane, 1955; Tsuchiya, Sugita, and Seki, 1976).

12.2.5 Toxicity and Effects

The toxicity of cadmium has been known for many years. Toxic effects can be traced to either acute or chronic exposure. In acute episodes, inhalation is more common than ingestion. The effects of inhalation exposure (Hise and Fulkerson, 1973) include: (1) shortness of breath; (2) chest pain; (3) headaches; (4) cough with bloody sputum; and (5) pulmonary edema. The lethal form can be cadmium fume (Princi, 1947), cadmium oxide (Beton et al., 1966), or dusts (Friberg, 1950), as case histories document (Friberg et al., 1974). Acute ingestion produces effects similar to food poisoning (Franc and Kleeman, 1941) but resulting in liver and kidney damage or death by renal failure (Hise and Fulkerson, 1973). Fortunately, cadmium also acts as an emetic — reducing absorption and toxicity (Hammons et al., 1978). Chronic exposure is primarily by ingestion because cadmium levels in food make this route more accessible in the general public. Chronic inhalation exposure occurs in industrial situations, with numerous case histories (Baader, 1952; Friberg, 1950; Lauwerys et al., 1974). Common symptoms are chronic bronchitis, emphysema, or proteinuria (Hammons et al., 1978).

The above effects are characteristic of the manner of exposure, but the following effects may occur regardless of route, because transport and storage are the same once cadmium is in the body. The kidney is particularly susceptible. Chronic exposure results in kidney accumulation, and after reaching a renal cortex level of 200 ppm, renal disruptions occur (Hammons et al., 1978; Nordberg, 1974). These include morphological changes, proteinuria, glucosuria, amino-aciduria, and formation of renal stones (Adams, Harrison, and Scott, 1969; Ahlmark et al., 1961; Bonnell, 1955; Kazantsis et al., 1963; Piscator, 1966; Smith and Kench, 1957). Failure of the kidney to function properly is the primary cause of disability or death from cadmium exposure. However, other toxic effects and debilitating associations have been suggested. Both animal and epidemiological studies have shown an association between cadmium intake and anemia (Decker et al., 1958; Fox and Fry, 1970; Friberg, 1950; Hise and Fulkerson, 1973). Liver function disruption (Axelsson and Piscator, 1966; Friberg et al., 1974) and testicular damage (Favino et al., 1968; Gunn, Gould, and Anderson, 1963) have also been indicated by similar studies as resulting from cadmium intake. In addition, cadmium has toxic effects on the nervous system (Friberg, Piscator, and Nordberg, 1971). In particular, cadmium interferes with synaptic transmission (Cooper and Steinberg, 1977; Kober, 1977; Smirnov, Byzov, and Rampan, 1954). Cadmium has been suggested as a cause of or factor in hypertension (Carroll, 1966; Friberg et al., 1974; Schroeder, 1965*a*). This association is based on animal studies and epidemiological correlations. However, there are also many studies discrediting or contradicting these correlations (Hunt et al., 1971; Lewis et al., 1972; Morgan, 1969; Porter, Miya, and Bousquet, 1974). The whole question is reviewed by Hise and Fulkerson (1973) and by Friberg et al. (1974). Another area in dispute is the association between cadmium and cancer. Again, studies have produced evidence supporting (Kipling and Waterhouse, 1967; Morgan, 1970; Morgan, Branch, and Watkins, 1971) and disputing (Koch, Smith, and McNelly, 1957; Mulay et al., 1971; Santoliquido, Southwick, and Olwin, 1976) the association. A complicating factor is the linkage of cancer, high cadmium levels, and cigarette smoking (Friberg et al., 1974). As with zinc, these associations of high cadmium levels with cancer and other diseases are circumstantial and may be a result instead of a cause.

The metabolic action of cadmium is most often cited as being enzymatic in nature. Several mitochondrial and extramitochondrial enzymes are inhibited by cadmium. Animal studies indicate that cadmium reacts with sulfhydryl groups resulting in: (1) blocked synthesis of adenosine triphosphate (ATP); (2) blocked conversion of ATP to adenosine diphosphate (ADP) by preferential binding to ATPase; and (3) interrupted transfer of electrons in the citric acid cycle (Berry et al., 1974). Additionally, cadmium substitutes for zinc in zinc-requiring enzymes, thereby altering these enzymatic activities (Griffin et al., 1973; Smith, 1973). This relationship to zinc is especially important considering the close physicochemical association of zinc and cadmium.

As a final example of cadmium toxicity, itai-itai disease shows how complex the analysis of trace-metal toxicity can be. Itai-itai is an epidemic cadmium poisoning in which elderly, multiparous Japanese women experienced renal dysfunction, osteoporosis, and osteomalacia (Hammons et al., 1978). Although at first credited solely to high-cadmium food and water levels (Friberg et al., 1974), recently it has been considered to be the result of low calcium, low Vitamin D, poor nutrition, and excess cadmium (Murata et al., 1970; Takeuchi, 1973). Thus, in analyzing cadmium toxicity, one must not forget how interrelated all trace-element metabolism is.

12.2.6 Demography

Epidemiological studies have revealed several trends in cadmium tissue levels. As a nonessential element, cadmium is normally absent or in low concentrations in fetal and juvenile tissues. The tissue concentrations increase with age until middle age (approximately 50 years), then decrease slightly (Elinder et al., 1976; Gul'ko, 1965; Hammer et al., 1973*b*; Johnson, Tillery, and Prevost, 1975; Perry et al., 1961; Tipton and Shafer, 1964). This trend holds true for all tissues except hair, which is more variable (Schroeder and Nason, 1969). Sex differences are often detectable in the quantity of stored cadmium, but the general trend is still true (Hammer, Colucci, Hasselblad, Williams, and Pinkerton, 1973; Petering, Yeager, and Witherup, 1971). Perry et al. (1961) report world geographical variation in cadmium levels with highest values occurring in Asians and the lowest values in native Africans. Caucasoid values were intermediate between these extremes regardless of their geographical location. Studies have shown only slight differences between rural and urban populations, with more variation in tissue levels due to industrial point source exposure than to urbanization (Anon., 1971; Eads and Lambdin, 1973; Hecker et al., 1974; Schroeder, 1974*a*). The strongest epidemiological correlation for cadmium is with cigarette smoking. Tissue concentrations are always higher for smokers, with the increase correlated to smoking intensity (Elinder et al., 1976; Hammer, Colucci, Creason, and Pinkerton, 1973; Lewis et al., 1972; Shuman, Voors, and Gallagher, 1974). No definite trends were identified for socioeconomic variables.

12.2.7 Analysis

The analysis of cadmium relies on the same basic techniques used in most trace-element analyses. These methods include atomic absorption spectrometry (flame and flameless), emission spectroscopy, neutron activation analysis, polarography, anodic stripping voltammetry, and x-ray fluorescence. The decision as to which method to use depends on the sample composition and size, the precision required, the equipment available, and the cost. Modifications abound in the literature for most methods that help eliminate sample handling or preparation problems, reduce interferences, and increase sensitivity. Reviews and comparisons of the various analytic methods can be found in Friberg et al. (1974, 1975) and in Hammons et al. (1978).

SECTION 13

COPPER, MAGNESIUM, MANGANESE, MOLYBDENUM, SELENIUM, TELLURIUM, AND POLONIUM

13.1 INTRODUCTION. RELATIVE TOXICITIES

The first five of the above are essential elements. Both deficiency symptoms from lack and toxic symptoms from excess can occur. With respect to deficiencies, Mertz (1970) states that "Severe deficiencies of trace elements with known or suspected function probably do not exist in countries with free circulation of foods. Therefore, acute, life-endangering symptoms cannot be expected, and attention must be diverted to subtle, metabolic change." Mertz discusses specifically the effects of long-term marginal deficiencies. Here we are more concerned with the effects of long-term excesses which would strain the body's mechanism of control. With respect to excesses in the environment, some sectors and some organnisms are particularly susceptible. A striking example of this is copper, which appears to be essential to all living forms (Schroeder et al., 1966). However, copper when added to water is the most toxic of the common heavy metals to fish. It appears that fish do not have a barrier to prevent copper from going directly through the gills into the blood. Schroeder (1965*b*) presents a table of the toxicities of some metallic and nonmetallic ions to fish in soft and hard water (hard water is protective). In soft water, toxicities ranged from 0.1 ppm for copper and cadmium, through 0.2 for beryllium, 1 for tin, 1.3 for iron, 2 for zinc and lead, 70 for molybdenum, 100 for selenium as selenite, 2400 for manganese, to 5000 for magnesium.

13.2 COPPER

13.2.1 Copper in the Environment

Copper was probably the first metal worked by man. Its use extends back 7000 to 8000 years (Schroeder et al., 1966). Copper alloyed with tin gave rise to an age, the Bronze Age. (Brass, an alloy of copper with zinc, was not known until Roman times.) Many artifacts were made of copper, including cooking utensils. Copper toxicity was recognized, and the Romans alloyed copper with lead for food and water utensils, not realizing that lead was the more insidious poison (Christian, 1969). Schroeder et al. (1966) mention the practice in India of tinning copper pots and pans to prevent contact of food with the copper. It is lamentable that up until only a few years ago some countries allowed the addition of copper to canned vegetables, such as peas and green beans, to maintain a green color. Copper is ubiquitous in the environment. The mean concentration in crustal rocks is 45 ppm. When leaching has reduced available copper to <10 ppm, deficiency occurs. As previously mentioned, excess copper is quickly toxic to organisms lacking barriers to absorption. Poor excretion also elevates the toxicity. Avian and mammalian resistance to copper is 100 to 1000 times greater than that of more primitive animals (Schroeder et al., 1966), and monogastric mammals (man, hogs) have higher resistances than do multigastric animals.

13.2.2 Intake by Man. Deficiencies and Excess

In man, copper intake is largely from foods and water, less from air, except in some industrial situations. It should be noted that the danger from copper smelting operations is not so much the copper but the arsenic and lead associated with it (Baker et al., 1977; Milham, 1977). Schroeder et al. (1966) present the following figures in ug of human intake and output of copper in a soft-water area with relatively uncontaminated air. Intake: food, 3200; water, 200; beverages, 300; air, 2; total, 3702. Output: urine, 60; feces, 3640; sweat, 2; total, 3702. Some excess copper may come from leaching of copper water pipes by soft water. Other sources are dusts, and particulates from burning of copper-containing materials.

A balance in copper intake is needed. While some effects of excess copper are mentioned in the next section, it may be noted that deficiencies of copper (and zinc and manganese) are associated with characteristic integumentary and skeletal abnormalities, congenital anomalies (particularly in the case of zinc), defects in growth and development, and abnormalities in sensory preception (Burch, Hahn, and Sullivan, 1975). Both deficiencies and toxic effects from copper in humans are relatively uncommon (Bremner, 1974). In agriculture, animals may suffer copper poisoning from contamination of feed with copper-containing pesticides or from grazing on plants growing on highly copper-bearing soils.

13.2.3 Absorption, Metabolism, and Chronic Toxicity

Copper is absorbed from the stomach and upper gut by at least two mechanisms (Burch, Hahn, and Sullivan, 1975). One process takes energy and probably represents absorption of copper complexes of amino acids. In the second process, copper is absorbed across the intestinal mucosa by binding to the copper enzyme superoxide dismutase and to metallothionein. Other dietary ingredients influence copper absorption, notably molybdenum and sulfate. Mechanisms of transport of copper from the gut lumen to the blood are not known in detail. Copper is transported in the blood, loosely bound to serum albumin (Cartwright and Wintrobe, 1964). Copper in the blood associates firmly with the hematopoietic enzyme ceruloplasmin. Copper in the blood is distributed to the liver, kidneys, spleen, bone marrow, and various other tissues; the highest concentrations are found in the liver and the brain (Cartwright and Wintrobe, 1964). The liver is the main storage organ for copper and is central in copper metabolism, governing excretion through the urinary system and controlling the synthesis of a number of the copper-containing enzymes.

Burch, Hahn, and Sullivan (1975) estimate the daily copper requirement to be 2.5 mg. The body content of copper is 80 to 120 mg. The ingestion of more than 15 mg of copper in a single dose produces nausea, vomiting, and diarrhea and intestinal cramps. Hemolysis may occur, and also jaundice, dilation of the central veins of the liver, hepatic necrosis, and in the kidneys tubular swelling and glomerular congestion. Higher doses may result in death. In chronic toxicity, there is an accumulation of copper in cell nuclei of the liver. Sudden release of this copper may give rise to a hemolytic incident. Hemolytic anemia is also the result of a familial disease of copper handling, Wilson's disease.

13.2.4 Disease States and Copper

Both high and low copper body levels are associated with a number of diseases (Koch, Smith, and McNelly, 1957; Olson, Heggen, and Edwards, 1958; Olson et al., 1954; Owen et al., 1977; Pedrero and Kozelka, 1951; Underwood, 1971, pp. 57-115). A causal relationship has generally not been found. There is some suspicion that increased copper may play some part in tissue changes in hardening of the arteries and heart disease (Morgan, 1972; Zinsser, Butt, and Leonard, 1957).

13.2.5 Analysis

Copper analysis for many years was chemical because the combination of copper with the chelating reagent diethyldithiocarbamate resulted in a characteristic color. Similar compounds were also used, and numerous variations of this analysis have been reported. But with the trend to multielement analysis, instrumental techniques are being used more frequently. These include flame photometry, emission spectroscopy, atomic absorption, x-ray fluorescence, neutron activation, polarography and inverse polarography, and others.

13.3 MAGNESIUM

Magnesium is one of the four "bulk" metals in the human body; the others are calcium, potassium, and sodium. It is important in electrolyte balance as a counter-ion to anions and is a cofactor in a number of enzymes. Its essentiality has been recognized since 1932 (Kruse, Orent, and McCollum, 1932; cited in Schroeder, Nason, and Tipton, 1969). "Standard man" contains 20 g of magnesium, the largest part of it intracellular. There is more magnesium than calcium in most soft tissues and about five times more than the next most prevalent intracellular cation, zinc. Schroeder, Nason, and Tipton (1969) in a review article asked the following questions: What is the distribution of magnesium in various organs and tissues of the human body? Do concentrations change with aging, or is homeostasis efficient throughout life? Do examples of tissue deficiency occur in human beings? If so, are they related to chronic diseases, especially cardiovascular?

What foods supply considerable magnesium? Do modern industrial food practices contribute to less than adequate intakes? To answer these questions. tissues from 197 subjects in the U.S. and 202 in foreign lands were analyzed, as well as levels of magnesium in a selection of foods. The tissue results appear in phase I of this report. The highest concentration was found in bone and the lowest in fat. Of the soft tissues, the omentum and adrenals, which are high in fat, had the lowest concentration, whereas larynx and aorta, which contain much calcium, were high. Concentrations in all tissues remained fairly constant after the first decade of life, except for a rise late in life in the aorta. Magnesium is efficiently used and efficiently retained by the body. Foods containing a high content of refined sugars and fats are low in magnesium, and Schroeder et al. make a case for the existence of a marginal dietary deficiency of magnesium in the U.S. Overt deficiency would appear in persons with impairment of renal reabsorption. An intake of 4 to 6 mg/day seems necessary for normal balance. There does not seem to be a problem with magnesium excess or toxicity.

13.4 MANGANESE

Manganese is omnipresent in living organisms and seems to be essential in all (Schroeder, Balassa, and Tipton, 1966). Plants accumulate manganese (and can be deficient in it) but animals do not. An efficient homeostatic mechanism for manganese appears to operate in all vertebrate and invertebrate animals. The body content of manganese in "standard" 70-kg man is 12 to 20 mg (Burch, Hahn, and Sullivan, 1975). This is 1/5 the content of copper and 1/100 that of zinc (Underwood, 1971, pp. 177-207). In man, manganese is concentrated in descending order in brain, kidney, pancreas, and liver (Burch, Hahn, and Sullivan, 1975), but other tissues also show characteristic levels of manganese. Within the cells, the highest concentration of manganese is in the mitochondria.

The normal intake of manganese in man is 2 to 5 mg/day. Higher doses are easily tolerated; in fact, manganese is among the trace elements showing the least toxicity. To show toxicity, long-term inhalation at high levels is needed. Such exposure may occur among manganese workers, for instance, in the steel industry. Symptoms of toxicity are psychoneurological disturbances similar to schizophrenia, and a Parkinson's disease-like shaking. A manganese pneumonia or bronchitis may also ensue. The risk of manganese to the general public is more from deficiency than excess, since diets may sometimes be deficient in manganese. Ingested manganese quickly appears in the bile. The liver is the key organ in the economy of manganese, the bile flow being the chief regulatory mechanism and main route of excretion of manganese. Some is excreted in the pancreatic secretion and also some by reverse passage into the intestines. Urinary excretion of manganese is minimal. Manganese to a large extent goes its own metabolic way, seeming to have little metabolic relation with other trace metals (Cotzias, 1960). Manganese is involved in synthesis of protein, DNA, and RNA (Burch, Hahn, and Sullivan, 1975), and also in neurohormone control and oxidative phosphorylation and lipid metabolism (Schroeder, Balassa, and Tipton, 1966).

Analysis of manganese has been somewhat difficult, hindering investigation of possible changes in blood manganese concentrations associated with specific disorders; however, use of modern instrumental methods such as neutron activation (Hahn, Tuma, and Sullivan, 1968, cited in Burch, Hahn, and Sullivan, 1975) has overcome this obstacle.

13.5 MOLYBDENUM

13.5.1 Molybdenum in Foods and in the Body

Schroeder, Balassa, and Tipton (1970) and Underwood (1971, pp. 116-140) have reviewed the biological implications of molybdenum. Knowledge of the tissue distribution, variations with geographic location, and the like have come from the extensive studies of Tipton et al. Tables of the molybdenum content of foods are given in Schroeder, Balassa, and Tipton (1970). Molybdenum is low in refined foods, and a marginal deficiency of molybdenum is a possibility with a poor diet. Molybdenum is essential, apparently to all forms of life, excepting some algae. It is necessary to all bacteria engaged in some part of the nitrogen cycle in the biosphere, particularly for the nitrogen-fixing bacteria. As a result of this, soils lacking molybdenum are generally barren. Molybdenum in the human body is part of four flavo-enzymes: two oxidoreductases, an aldehyde oxidase, and xanthine oxidase (Schroeder, Balassa, and Tipton, 1970). Deficiency of molybdenum may result in xanthine calculi and in other perturbances of purine metabolism. Molybdenum is found mainly in the liver, kidney, adrenals, and omentum, which likely reflects its association with the above-named enzymes. It hardly appears in the blood — the concentration in over 75% of 210 samples from all over the U.S. was less than 0.5 μg/100 ml (Allaway et al., 1968). There is a complex interaction between copper, molybdenum, and sulfate, which is particularly important in animal nutrition. Molybdenum and sulfate are antagonistic to copper and can either increase or decrease the copper status of an animal, depending on the relative intake. There is some evidence (mentioned in Schroeder, Balassa, and Tipton, 1970) that molybdenum can enhance the anticaries activity of fluorine. Criticisms of this view are reported by Underwood (1971). The balance of molybdenum, as given by Schroeder, Balassa, and Tipton (1970) based on extensive studies, is as follows: intake in μg: food, 335 (210 to 460); water, 2.8 (0 to 136); air, <0.1; total, 335 (210 to 595). Output in μg: urine, 190 (116 to 252); feces, 125 (90 to 160); sweat, 20; hair, 0.01; total, 335 (226 to 462). The body content of molybdenum goes up to about age 20 then slowly declines.

13.5.2 Sources and Toxicity of Molybdenum

As seen in the balance given by Schroeder, Balassa, and Tipton (1970), intake in man is chiefly through food, with more possibility of deficiency than of excess. Molybdenum is found in industrial smokes and in oils. Dusts from metal-working operations may also be a source. The toxicity of molybdenum is more of a problem for animals than it is for humans. Among domestic animals, sheep and cattle are least tolerant, whereas horses and pigs are quite tolerant. Manifestations of toxicity are weight loss and retardation of growth, diarrhea, anemia, skin deficiencies, including alopecia, other connective tissue changes, and deficient lactation in females and testicular degeneration in males.

13.5.3 Analysis

Analysis of molybdenum has been by wet chemical methods, but more recently by instrumental methods, among which neutron activation and atomic absorption spectrometry are prominent.

13.6 SELENIUM

13.6.1 Introduction. Selenium Toxicity

As stated by Schroeder, Frost, and Balassa (1970), selenium is the "least abundant and the most toxic of the elements known to be essential for mammals." These authors also state: "Selenium toxicity, from whatever source, produces loss of fertility, congenital malformations, defects in the eyes, small litters, and emaciated young; therefore it is teratogenic. It is interesting that both deficiency and toxicity of selenium cause retarded growth, muscular weakness, infertility, and focal necrosis of the liver."

Areas of high selenium (plants growing in alkaline soils, where selenium may be in excess) are of concern in farming and ranching. Cattle, hogs, horses, and sheep, which consume high-selenium grains and plants, suffer loss of hair and hooves, lassitude, anemia, joint stiffness, and liver and heart damage. Selenium is akin to sulfur and replaces it in proteins, in the sulfur-containing amino acids, and in their metabolites. Symptoms of selenium toxicity in man include discolored and decayed teeth, yellow skin color from selenium-caused bilirubinemia, skin eruptions, chronic arthritis, atrophic brittle nails, edema, and gastrointestinal disorders. Selenium, fortunately, does not accumulate — above a certain excess, excretion keeps pace with intake. However, this level is a toxic one, and some irreversible harm may ensue before intake can be brought back to normal. Schroeder, Frost, and Balassa (1970) state that overt human toxicity has occurred only in persons living in seleniferous areas and consuming local food. It may be noted that retention of organic selenium in tissues is greater than that of inorganic forms, reflecting the more circuitous metabolic pathways taken by the organically bound selenium.

13.6.2 Sources

Selenium is produced largely as a by-product of copper refining. Several methods are used. The U.S. is a leading producer, followed by Canada, Japan, and Sweden. U.S. production in 1973 was 627,000 lb (National Research Council, 1976): 530,000 lb was imported. U.S. primary industrial demand was 1,200,000 lb. Selenium has multiple uses, and numerous compounds are used: in electronics (photoconductive devices, rectifiers, etc.), in steel making, in pigments, in glasses and ceramics, in catalysts, in solvent formulation, in oils, etc. Selenium is associated with sulfur, and wherever sulfur is burned and emitted into the atmosphere, selenium can be expected to occur also, at the ratio 1/10,000 (Schroeder, Frost, and Balassa, 1970). The selenium tends, however, to be in a relatively nonpolluting, particulate form. According to the NAS publication on selenium (National Research Council, 1976), total atmospheric industrial emission of selenium was estimated for 1970 at 2,430,000 lb (this is higher than the domestic primary production, which was 1,005,000 lb for 1970). Burning of coal accounted for 62% of the total, or 1,500,000 lb. An almost equal amount, 1,400,000 lb, was derived from coal as solid waste. Losses of selenium in nonferrous mining, smelting, and refining operations accounted for 26% of the total, and the remainder was derived from precious-metal refining operations, glass making, and burning of fuel oil. Total solid waste for 1970 was 6,980,000 lb; 3,600,000 lb of this was derived from mining and milling, where selenium was not the primary object of the operations. Given proper dispersal, man-made concentrations of selenium are considered to be trifling in comparison with the natural concentration. Incidentally, a chief natural source has been volcanic action over geologic time, with distribution occurring by the operation of the other geologic and natural processes.

13.6.3 Body Burden and Distribution. Role of Selenium in Normal Metabolism

Schroeder, Frost, and Balassa (1970) give the calculated body burden of selenium as 14.6 mg (range 13 to 20 mg). The concentration in animals is two to three times higher. In man, the highest concentration is in the kidneys, followed by the glandular tissues, especially pancreas and pituitary, and then the liver (Underwood, 1971, pp. 323-368). Muscles, bones, and blood are low, and adipose tissue is very low. Blood concentrations are erratic. More selenium is in the erythrocytes than in the plasma. Cardiac muscle is higher than skeletal muscle. The balance of selenium, as given by Schroeder, Frost, and Balassa (1970), based on persons living in the northeastern part of the U.S., is: Intake in μg: food, 60 to 150; water, <1; air, <1. Output in μg: urine, 20 to 50; feces, 8 to 30; sweat, hair, expired air, etc., 32 to 80. As an essential element, selenium appears to be involved in normal growth, muscle function, integrity of the liver, and fertility (in connection with vitamin E). Selenium is an integral part of the enzyme glutathione peroxidase (National Research Council, 1976), which destroys peroxides in the organism. Selenium has multiple metabolic pathways, depending on the chemical form, and nutritional and toxic effects also reflect chemical form. Aspects of this are reviewed by Allaway (1973).

13.6.4 Selenium in Food. Management of Natural Selenium

Allaway (1973) gives a map of the regional pattern in the U.S. of selenium concentration in crops and in the muscle of pigs produced in specific locations. The latter figures ranged from 1.89 ppm in dry muscle of hogs raised in South Dakota—Minnesota to 0.163 ppm in New York State. The Northeastern—Great Lakes region is low in selenium, as are the Southeastern seacoast and the Pacific Northwest. Most of the U.S. is "adequate," with some regions variable and some with localized areas of high selenium. Generally, the areas reflect the occurrence of forest (acid) and prairie and desert soils (neutral to alkaline). As soils become more acid, selenium becomes less and less available biologically. Considering the possibility of human exposure to excess selenium from eating of animal products, and the large area of "adequate" selenium concentration, Schroeder, Frost, and Balassa (1970) recommend that selenium should not be added routinely to animal foodstuffs, but only where clear deficiencies exist. As for excess, some palliatives of selenium toxicity have been developed, but management generally consists of keeping stock away from high-selenium areas. Schroeder, Frost, and Balassa (1970) consider that with modern food distribution, human deficiency of selenium does not occur, except in extremely malnourished children. Excesses would be sufficiently diluted by the food distribution system.

13.6.5 Selenium and Carcinogenesis

Given in various forms — organic, inorganic, dusts, vapors — selenium has been shown to be carcinogenic in rats and other experimental animals, but a causal connection with human cancer has not been shown. The question is confused, because selenium, particularly in the form of selenite and some organic selenium compounds, has also been shown to be protective against certain cancers in experimental animals; and with respect to humans, Shamberger and Willis (1971) and Shamberger et al. (1973) have presented epidemiological studies indicating a sharply lower death rate from carcinoma of the digestive tract in areas of high environmental content of selenium than in areas of low selenium content in the U.S. The effect of selenium was attributed to the antioxidant power of its compounds. The question of carcinogenicity of selenium has been discussed by Schroeder, Frost, and Balassa (1970), Underwood (1971), and Cooper and Glover (1974), and is particularly well treated in a publication of the National Academy of Sciences (National Research Council, 1976). The impression one gets is that selenium does not present a carcinogenic hazard to humans and in fact may have some anticarcinogenic effect.

13.6.6 Analysis

Virtually all the methods of analysis mentioned in this report have been used for the analysis of selenium: chemical, fluorometric, atomic absorption, gas chromatography, neutron activation, etc. The fluorometric method has had wide application in biological studies. A good proportion of selenium compounds are volatile or are subject to enzyme action, and so care must be exercised in handling to avoid losses and redistributions. The subject of selenium analysis has been treated summarily in the NAS publication on selenium (National Research Council, 1976) and fairly extensively by Cooper (1974).

13.7 TELLURIUM AND POLONIUM

These elements are in the same chemical series as oxygen, sulfur, and selenium. Polonium has 27 isotopes, from atomic mass 192 to 218. All are radioactive. Polonium-210 is the most readily available. While it is present in low quantity, it is intensely radioactive (alpha emitter). Along with ^{210}Pb it is a main component of natural background radiation. Its use in industry is strictly controlled. Polonium-210 appears in cigarette smoke (Ferri and Baratta, 1966) and in human tissues (Baratta, Apideanakis, and Ferri, 1969). The main source, however, is food (Ladinskaya et al., 1973). It is of concern in uranium mining and processing.

Tellurium, similarly to selenium, is obtained as a by-product of the refining of other metals such as copper, lead, and particularly silver and gold. Its chemistry and uses are similar to those of selenium. The amount used is considerably less. No biological function for tellurium has been found, except perhaps as an antagonist to selenium. Studies of its occurrence in foods and in human tissues have been reviewed by Schroeder, Buckman, and Balassa (1967). The body burden of tellurium of "standard man" was calculated to be about 602 mg, of which about 540 mg is in bone, the rest being in various soft tissues. This puts the content of tellurium higher than that of all the other trace elements except iron, zinc, and rubidium. High levels in some processed foods indicated that some contamination from industrial sources may occur. Tellurium in the body seems not particularly deleterious, and Schroeder, Buckman, and Balassa (1967) speculate that natural tellurium is present as the relatively innocuous tellurate. Excretion of tellurium compounds seems to keep up with intake; there does seem, however, to be a slow accumulation with age in bones and liver.

SECTION 14

ARSENIC, ANTIMONY, AND THALLIUM

14.1 ARSENIC

14.1.1 Sources and Uses of Arsenic

Schroeder and Balassa (1966) have reviewed aspects of arsenic in the biosphere, from ancient times to the present. Arsenic (and antimony) were known in antiquity in the form of their compounds, which were used both medicinally and as poisons. Use of arsenic increased greatly in the Industrial Age, but arsenic in the environment is diminishing at present due to replacement of arsenical pesticides with other, mainly organic, ones. Arsenic continues, however, to present localized situations of concern. Arsenic exists naturally in some well waters in toxic excess (Goldsmith et al., 1972; Whanger, Weswig, and Stoner, 1977; see also Dubos, 1968). Arsenic in the earth's crust is largely in the form of arsenate; however, arsenides also exist in deposits. Arsenic may be present in soils in concentration sufficient to cause manifestations of toxicity. Industrially, there are emissions of arsenic compounds near smelters (Baker et al., 1977; Milham, 1977) and from metal treatment processes. Again, even though use of arsenicals in agriculture, forestry, and horticulture has declined, there are still episodes of arsenic poisoning, often from household use of arsenicals (U.S. Environmental Protection Agency, 1977*a*). Some arsenic enters the air from burning of coal (Bencko and Symon, 1977*a*,*b*). These authors found hearing loss, high incidences of respiratory diseases, gastrointestinal disturbances, and skin and eye irritation among children living near a power plant burning high-arsenic coal, the arsenic being mainly in the form of arsenic trioxide in the solid phase of the emission.

14.1.2 Toxicity and Metabolism of Arsenic Compounds

Elemental or metallic arsenic occurs naturally, and according to Schroeder and Balassa (1966) is not toxic. Nagai et al. (1956) discussed an epidemic of poisoning in infants which had resulted from consumption of powdered milk contaminated with arsenic. The toxicity of arsenic compounds as seen in these poisonings was as follows: arsenious acid < arsenic acid < arsenite < arsenate. As pointed out by Schroeder and Balassa (1966), arsenite combines with -SH groups of proteins, whereas arsenate does not. Furthermore, arsenate is less readily absorbed and is relatively quickly excreted, via the kidneys, whereas arsenite is more easily absorbed, is mainly excreted in the bile, does more damage, and is retained longer. Organic arsenites are generally more inhibitory of the action of various enzymes than is inorganic arsenite. Arsenic may be an essential element, but due to its ubiquity, it has been difficult to test whether this is true or not. In cases of high arsenic intake, allergies, skin disease, neurological disorders, blood protein abnormalities, goiter, and other symptoms may occur, and there is a chance of skin cancer, although evidence on this last point is conflicting (Lisella, Long, and Scott, 1972).

The gas arsine, AsH_3, is very toxic, and the antimony analog stibine, SbH_3, is even more so. These gases would hardly be encountered, except industrially. Uses of arsenic are multiple, and they are highly dissipative. Whereas arsenic already naturally in the environment cycles through it without apparent harm to living things, the additional arsenic released to the environment from smelters, pesticide application, wastes, and the like can increase concentration in certain areas to levels which are toxic to both plants and animals. The reasonable conclusion is monitoring and control where necessary.

14.2 ANTIMONY

The chemistry and uses of antimony are similar to those of arsenic. A major use is to increase the hardness and mechanical strength of lead, as in batteries, type metal, and bearings. Antimony is common but less abundant than arsenic, and its levels of use and potential for pollution are less. However, antimony in industrial smokes may cause lung disease (Bowen, 1966). Analysis of arsenic and antimony is by either chemical or instrumental means.

14.3 THALLIUM

Thallium, element No. 81, lies between mercury, 80, and lead, 82, in the periodic table. It is the last number of the series boron, aluminum, gallium, indium, thallium. Thallium was discovered in 1861, but for quite a time was only a chemical curiosity. Thallium acetate taken orally at near fatal doses was used as a depilatory, and also for treatment of skin infection and as an adjunct in tuberculosis care. Thallium sulfate has been much used as a rodenticide and ant killer; fatal accidents have occurred through misuse. The use of thallium in pesticides was banned in 1972 in the U.S. Legitimate uses, under proper control, are in specialty glasses, in photoconductive and other electronic devices, and in chemical reactions, as in manufacture of rare organics. Emsley (1978) takes the position that "Thallium has no place in civilized society outside the chemical laboratory," the context of his remarks indicating that he means "properly controlled manufacturing chemical laboratory." Some thallium is produced as a by-product in the roasting of pyrite ores to make sulfuric acid; most comes from treatment of fine dusts from lead and zinc smelters.

Thallium and its compounds are highly toxic, and poisoning may ensue by absorption from inhalation, ingestion, or through the skin. As mentioned in the introductory parts of this report, the body treats thallium as it does potassium as far as absorption, compartmentation, and excretion are concerned. The chemistry of trivalent thallium, however, resembles that of aluminum. According to Emsley (1978), naturally occurring thallium poses no threat to the environment. The annual world production of thallium in 1974 was 15 tons (mercury, 9240 tons; lead, 3,430,000 tons). Thallium concentrates in the brain (Tewari, Harpalani, and Tripathi, 1975), and neurological disturbances are part of the thallium toxicity syndrome. An extensive report on environmental exposure to thallium has been presented by Carson and Smith (1977). The average body burden of thallium as given by these authors is about 0.14 mg, and intake (mainly from foods) and excretion (through urine and feces) are about 2 μg/day. According to Heyndrickx (1957; cited by Bowen, 1966), there is some accumulation of thallium by the kidney.

Analysis is by both chemical and instrumental means.

SECTION 15

CHROMIUM, COBALT, NICKEL, VANADIUM, AND BERYLLIUM

15.1 CHROMIUM

Chromium is 17th in abundance among all the elements, not counting the gaseous ones, and is 4th in abundance of the 29 elements of biological importance (National Research Council, 1974). Chromium is not found in its elemental form in nature, and neither chromium metal nor chromium compounds were used or known in antiquity. Chromium was discovered in 1797 by Vauquelin. Chromium compounds tend to be colored, and this property gave rise to the name. Chromium is an essential element in animals and apparently also in plants, and is found in almost all living things. In man, chromium is part of the glucose tolerance factor (Mertz, 1974) and also appears to have a part in the activity of enzymes involved in the metabolism of sugars, fats, and amino acids. The level of chromium in "standard man" was reported in 1959 to be "less than 6 mg" (Schroeder, Balassa, and Tipton, 1962*a*). A later figure, probably nearer the correct value, is 1.72 to 1.86 mg (Schroeder, 1970*a*). The discrepancy may arise from the lack of sensitivity and other difficulties of some earlier-used methods of analysis for chromium. The amount of chromium ingested per day by subjects selecting their own diets was found by Schroeder (1970*a*) to be 200 to 400 μg. Ingested chromium clears the blood rapidly and is distributed in the soft tissues. Chromium does not accumulate, except slowly in the lungs (Schroeder, 1970*a*), reflecting retention of insoluble trivalent chromium.

Chromium in trivalent form is relatively nontoxic, whereas compounds of hexavalent chromium tend to be toxic and irritating. Chromium in the earth's crust is mostly in the form of chromic oxide (trivalent), and the greatly lesser toxicity or potential for deleterious effects of trivalent, as compared with hexavalent chromium compounds, is therefore an example of Schroeder and Balassa's rule (Schroeder and Balassa, 1966), which states or observes that generally the most stable natural valence of an element, the one found normally in soil and water, is the least toxic. The toxicity of hexavalent chromium compounds reflects largely the oxidizing power of the hexavalent state. Thus, as noted by Schroeder (1970*a*), workers exposed to trivalent chromium suffer little if any effects, whereas those exposed to hexavalent chromium tend to develop skin and respiratory disorders. Sensitization may ensue, and there is evidence that sensitization provoked by hexavalent chromium may carry over to the trivalent form (National Research Council, 1974). A serious long-term danger is the production of lung cancer. The latent period is long, and the cooperation of other factors in causing the cancers is not excluded.

Chromium is used in chrome plating and in alloys, and chromium compounds are used as coatings, as dyes or dye adjuncts, in leather tanning, as catalysts, etc. Pollution arises primarily from industrial use and product use. Chromium is also found in cements and asbestos and is emitted into the air by burning of coal and wood.

Schroeder, Balassa, and Tipton (1962*a*) and Schroeder (1970*b*) found chromium in the air in U.S. cities generally on the decline since 1954—59, with, however, increases in a few. Burning of coal seems to be a major source. Aside from the question of localized areas of concern, the conclusion of reviews on chromium (National Research Council, 1974; Schroeder, Balassa, and Tipton, 1962*a*; Schroeder, 1970*b*; Towill et al., 1978; Underwood, 1971, pp. 253-266) is that while chromium presents an industrial problem, it does not present a problem to the general population. One of the authors (Pierce) of the review by Towill et al. (1978) stresses, however, the need for improvement in analysis of chromium and for further research on chromium metabolism and pathways of chromium in the environment.

15.2 COBALT

Cobalt has been used for centuries in the form of its salts for production of permanent blue colors in glass, tiles, enamels, etc. It was discovered as an element in 1735 (Weast, 1976). While cobalt and its compounds are not usually very toxic, it is possible that cobalt was a contributing factor to skin lesions and other disorders affecting miners of arsenical silver-cobalt ores and also workers exposed to fumes from smelters in the late Middle Ages. In modern times, a chronic pneumonitis of workers in the tungsten carbide and Carboloy alloy industries has been attributed to the presence of cobalt, and an allergic dermatitis has been shown to be due to contact with cobalt and its compounds. The TLV for cobalt metal fumes and dust is 0.1 mg/m^3 (ACGIH, 1971). Cobalt acetate added to beer to control foaming has been associated with a myocardial insufficiency affecting heavy beer drinkers, but cobalt as the cause has not been proven. Excess cobalt taken orally causes polycythemia, with hyperplasia of the bone marrow (Schroeder, Nason, and Tipton, 1967). Small doses cause vasodilation, and cobalt chloride has been used experimentally to lower blood pressure in hypertensive patients and to reduce the need for anti-hypertensive drugs (Perry and Schroeder, 1954; cited in Schroeder, Nason, and Tipton, 1967). The tolerated-to-toxic dose of cobalt orally in man is 2 to 7 mg/kg body weight/day.

Reviews on cobalt stress its essentiality in biological systems (e.g., Schroeder, Nason, and Tipton, 1967; Underwood, 1971, pp. 141-169). Cobalt is not evenly distributed in the earth's crust, and areas of deficiency, affecting especially grazing animals, occur. Cobalt is the central atom in the porphyrin-like corrinoid structure of vitamin B_{12} (cobalamin). This vitamin is synthesized by bacteria. As reported by Schroeder, Nason, and Tipton (1967), "one microgram of vitamin B_{12} per day containing 0.0434 μg cobalt can make the difference between life and death from pernicious anemia," making this amount "probably the smallest effective dose for any compound known today on a weight basis." Cobalt likely has also some other essential biological functions. As mentioned by Schroeder, Nason, and Tipton (1967), cobalt is found in all tissues but has a predilection for liver and heart. It occurs in newborns and children and shows no tendency to accumulate with age. The body level and flux of cobalt are about the same as for chromium. However, due to the widespread occurrence of cobalt in foods, deficiencies are not usually seen. Cobalt is detectable in the air of industrial cities, apparently coming mainly from the burning of coal and oil. Schroeder, Nason, and Tipton (1967) found cobalt in snow and considered the source to be fuel burned in automobiles.

Cobalt does not seem to pose a problem to the general population.

15.3 NICKEL

Nickel can give a number of toxic effects (National Research Council, 1975, pp. 97-128), but ingested nickel shows a low toxicity due to poor absorption. The element is generally considered relatively nontoxic. Nickel occurs regularly in soils and plants in concentrations substantially higher than those present in animal tissues and fluids (Underwood, 1971, pp. 170-176), and occurs in foods at levels generally sufficient for good nutrition. Nickel activates a number of enzymes (Schroeder, Balassa, and Tipton, 1962*b*; Schroeder, 1970*a*; National Research Council, 1975, pp. 62-96; Underwood, 1971, pp. 170-176) and is an essential element (Mertz, 1974). It is found in newborns. Homeostasis for nickel is good, and nickel does not accumulate with age. It occurs in most tissues. The body load is about 10 mg. According to Mertz (1974), nickel, like vanadium (also an essential element), is particularly important in lipid metabolism. Concern over nickel arises primarily from emissions of nickel into the atmosphere from industrial processes, from the burning of coal, from the burning of fuel oil (residues of the nickel used as catalyst), and from automobiles. Schroeder in 1970 (Schroeder, 1970*a*) recommended the elimination of nickel additives from gasoline, and the NAS review of 1975 (National Research Council, 1975, pp. 4-61) reported that based on information received from the petroleum industry, this had been achieved. Some nickel compounds encountered industrially are extremely toxic, for example, nickel carbonyl, used in the Mond process for obtaining nickel metal. The TLV for this compound is 0.001 ppm, and for nickel dust or fumes and soluble nickel salts it is 1 mg/m^3; there is evidence that this limit should be lowered, since it may not be low enough to prevent dermatitis or sensitization (ACGIH, 1971). Nickel dust has been shown to be carcinogenic in animals and to produce cancers of the respiratory system in workmen (ACGIH, 1971).

The NAS review document (National Research Council, 1975, pp. 4-61) reported figures for nickel in the air over a number of U.S. cities. Recommendations are presented concerning monitoring of airborne nickel, measures to promote industrial health and safety, epidemiologic investigation, toxicology of nickel compounds, metabolism of nickel, and dermatologic investigations.

15.4 VANADIUM

Vanadium is an essential element (Mertz, 1974), as shown by the production of deficiency symptoms in animals. A main effect of vanadium is on lipid metabolism. Vanadium, industrially, is considered somewhat more toxic than some of the other trace metals (ACGIH, 1971; see, however, Schroeder, Balassa, and Tipton, 1963, for a contrary view), pentavalent vanadium being more toxic than other forms. The TLV for V_2O_5 dust is 0.5 mg/m^3 and for V_2O_5 fume is 0.05 mg/m^3. By way of comparison, concentrations of a fraction of a μg/m^3 have been reported in the air of most cities, with some in excess of 1 μg/m^3 (Smith, 1972). As seen industrially, inhalation of vanadium dust causes irritation of the respiratory tract, emphysema, edema, bronchial pneumonia, and other respiratory disorders.

With respect to vanadium in the air generally, Schroeder (1970*b*) lists it among the "relatively nontoxic" elements; others are titanium, zirconium, niobium, and strontium. These are in contrast to nickel, beryllium, cadmium, tin, antimony, lead, and bismuth, which are listed as elements of "innate toxicity." Schroeder (1970*b*) and also Smith (1972) cite evidence critical of earlier reports of deleterious effects of vanadium; one point of criticism was that vanadium was not the only element present in the incidents of exposure studied.

Vanadium is ubiquitous in the earth's crust, and considerable vanadium occurs in foods, albeit in an erratic manner (Underwood, 1971, pp. 416-424). Homeostasis for vanadium is good. The level of vanadium in the body is reported to be from 10 to 25 mg. The experimental finding that administration of vanadium salts reduces hardening of the arteries in experimental animals is compatible with the involvement of vanadium in lipid metabolism; furthermore, vanadium workers show lower cholesterol levels than their compeers in the general population. On the other hand, vanadium in excess inhibits synthesis of choline, and this is not desirable. Details of the effects of vanadium on lipid metabolism may be found in Underwood (1971).

Vanadium concentrations are high in fossil fuels, and the pollution potential for vanadium results largely from burning of coal and fuel oil; however, there are numerous lesser inputs from the widespread use of vanadium. Smith (1972) lists vanadium among five elements of potential concern with respect to pollution; the others are chromium, manganese, nickel, and arsenic. Smith makes the point that control of particulates in general will reduce vanadium emissions, along with emissions of other elements of concern. Desulfurization of oil removes vanadium to the same extent as sulfur.

15.5 BERYLLIUM

15.5.1 Absorption, Toxicity, and Body Distribution

Beryllium compounds tend to have a sweet taste, accounting for an early alternate name for beryllium: glucinum. Beryllium is very toxic if it gets into the blood, for instance, through skin abrasion or through a wound. However, absorption of beryllium compounds in the alimentary tract is poor, and even soluble compounds of beryllium may not be very toxic when ingested. The chief hazard of beryllium is from inhalation; poisoning may be acute or chronic. Acute beryllium poisoning is characterized by a delay period of a week or two following exposure to a critical dose; then respiratory involvement and distress and pneumonitis ensue; the outcome may be fatal. Chronic beryllium poisoning may have a latent period of 20 to 25 years. A lung disease similar to sarcoidosis develops. Other effects are dyspnea, chest pain, renal stones, cough, fatigue, cardiac insufficiency, pneumothorax, liver and spleen enlargement, and other debilitating malfunctions. Radiology of the lungs is particularly important in diagnosis (Chamberlin, 1959), the lungs showing a diffuse pattern of deposition of beryllium. Stress may bring on symptoms of the disease. Clary and Stokinger (1973) have proposed that a triggering event, such as surgery, infection, etc., can cause adrenal imbalance resulting in translocation of beryllium from wherever stored to the liver, with resulting inflammation, lysosomal instability, lysosomal rupture, cell death, and onset of the disease. Beryllium goes to bone as the ultimate sink (Tepper, 1972) but also goes to the lysosomes and to cell nuclei (Witschi and Aldridge, 1968; Needham, 1974). Along with other toxic effects, beryllium has been shown to be a pulmonary carcinogen in the rat and other animals, by a variety of routes of exposure (Vorwald, Reeves, and Urban, 1966; Groth, Komineni, and Mackay, 1978, cited in Wagoner, Infante, and Mancuso, 1978), and the presumption is that beryllium is a carcinogen in man also; however, it has not been easy to establish a definite cause and effect relationship. Groth, Stettler, and Mackay (1976) have studied the interactions of mercury, calcium, selenium, tellurium, arsenic, and beryllium as relating to the ionization potentials of these elements and their abilities to form intermetallic complexes, complexes with organic molecules bearing a variety of functions, and eventually ultimate-carcinogen complexes with nucleic acid bases in RNA and DNA. Studies such as these may shed light on possible causation of cancer by beryllium. In the same way that the toxicity of beryllium was at first denied and then later accepted, there has also been some reluctance to admit a human carcinogenic potential for beryllium. A description of the situation as seen from one viewpoint is given by Wagoner, Infante, and Mancuso (1978), who cite epidemiological evidence of the association between exposure to beryllium and the incidence of cancers. One difficulty in demonstrating the carcinogenic capacity of beryllium in man is that significantly exposed people die of berylliosis before the time a cancer would appear. In any case, exposure to beryllium is dangerous enough to have resulted in the setting of a TLV of 2 $\mu g/m^3$ for the ambient atmosphere in the work place and of 0.01 $\mu g/m^3$ for neighborhood or community air (ACGIH, 1971). Schroeder (1974*c*) has considered beryllium to be the most toxic trace metal, the order of toxicity of beryllium with respect to some other metals of concern being beryllium > cadmium > lead > antimony > mercury. It is further noted that the first three are cumulative in the human body, whereas the last two are fairly readily excreted.

15.5.2 Sources, Uses, and Consumption of Beryllium

Beryllium is present in coal probably as beryl (Tepper, 1972), and the chief input into the air is from this source, but concentrations are not high enough to be of concern. Other sources are from industrial operations and from dispersion of beryllium-containing products. The chief area of concern remains the workplace. In industry, beryllium oxide, beryllium fluoride, and beryllium sulfate are toxic, whereas beryl (beryllium aluminum silicate) is not (Schroeder, 1974*c*). It is not known whether the form of beryllium in air from coal can cause berylliosis. The review of Tepper (1972) lists sources, uses, and industries in which there are particular hazards, and discusses the pharmacology of beryllium, clinical aspects of berylliosis, and assay and monitoring and industrial hygiene. Beryllium is a very useful metal, and its use is increasing. Consumption of beryllium in recent years has been about 300 metric tons, about 33% of this as the metal, 50% as Be-Cu alloys, 10% other alloys, 5% ceramics, and 2% miscellaneous. Of this amount, 45 to 68 metric tons were produced in the U.S. Annual domestic consumption is projected to increase to approximately 1500 metric tons by the year 2000, and about half the ore is expected to be mined within the U.S. (Heindl, 1970).

SECTION 16

OTHER ELEMENTS

We have discussed the chief elements of concern, within the guidelines of this project. This leaves, however, almost 50 elements; in all, a good part of the periodic table. There are TLVs on most of these, and some are more or less toxic — for instance, indium, 0.1 mg/m^3; iron salts, 1 mg/m^3; silver, 0.01 mg/m^3; platinum, 0.002 mg/m^3; osmium tetroxide, 0.002 mg/m^3; some tin salts, 2 mg/m^3; and so on. None of these are of concern to the general population. Sometimes, however, technological change will increase the environmental levels of an element to the point of possible concern; for instance, the introduction of platinum and other rare metals into the environment through use in automobile exhaust catalyzers, or increasing use of elements such as germanium and gallium as technology advances. Some of the elements not discussed specifically are essential — examples are tin and silicon (Mertz, 1974; Schwarz, 1974); strontium may have a biological role; zirconium may have a biological function, etc.

We have not considered elements such as sodium, potassium, phosphorus, calcium, etc., which are the so-called "bulk elements" in the biosphere, even though some of their compounds in excess may be deleterious in the environment; nor have we considered pollutants such as ozone, sulfur oxides, nitrogen oxides, etc., which do not leave residues in the body. We have also not considered compounds of the elements nor radioactive pollutants.

Most air pollution results from burning of materials, particularly fossil fuels. As mentioned in connection with vanadium (Smith, 1972), control of particulate emission in general will control dispersion of a considerable number of elements.

Besides the information on elements and compounds in the TLV documentation (ACGIH, 1971 and supplements), a listing of the properties, sources, uses, and physiological and toxic effects of metals, excluding lead, is given in the chapter by Stokinger in the treatise "Industrial Hygiene and Toxicology" (1963). A chapter on the biogeochemistry of the elements in the book by Bowen (1966) on "Trace Elements in Biochemistry" gives occurrence and levels in soil, water, plants, and animals, and describes the functions and toxicity of most of the elements. An excellent overview of environmental pollution is given in the book of that name by Hodges (1973). Physical and chemical principles are particularly considered. Interaction and interrelations of elements are important, and aspects of this, along with other topics, are covered in the volume edited by Nordberg (1976) on "Effects and Dose-Response Relationships of Toxic Metals."

A report by Matti, Witherspoon, and Blaylock (1975) deals with cycling of mercury and cadmium as typical pollutants in the environment. Lindberg et al. (1975) have discussed the mass balance of trace elements in a watershed, reflecting input from coal-fired steam plants.

The public health aspects of metals in the environment and their effects on the human body have been discussed by Schroeder (1974*b,c*). Tables of clearances of essential and nonessential metals and tissues in which they accumulate, when this is the case, are given, as are tables of U.S. industrial consumption, amounts in the human body, in the earth's crust, and in seawater, amounts added by weathering and by combustion of fossil fuels, urban air concentrations and estimates of maximal intakes by inhalation, levels in water and in ponds and exposures through use, and a listing of processes which are sources of introduction of metals into the environment.

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